CHAPTER 179

Comorbid Medical Emergencies During Pregnancy

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PRINCIPLES

The physiologic changes that occur in pregnancy may exceed the patient's underlying compensatory mechanisms, resulting in initial symptom onset or rapid decompensation of medical illness during pregnancy. Certain chronic medical conditions also pose a serious threat to the mother's health or result in a poor fetal outcome. Finally, some medical illnesses result in a difficult delivery or the need for special resuscitation measures in the neonate.

The incidence of pregnancy in chronically ill patients has been increasing because of improved survival of patients with diseases such as diabetes, epilepsy, renal failure, obesity, and various cancers. Also, the demographics of pregnancy are changing in that maternal age at the time of first pregnancy is increasing. Advances in assisted reproduction, including in vitro fertilization and oocyte donation, have made it possible for older women—including those who are postmenopausal—to become pregnant. Older pregnant women experience an increased rate of antepartum and intrapartum complications and are more likely to have comorbid conditions such as cardiovascular disease.

The recognition of an unexpected or even expected pregnancy may occur in the setting of the emergency department (ED), and many interventions are time-sensitive, mandating treatment in the ED. All emergency clinicians should have an understanding of critical diagnostic and treatment possibilities when encountering a pregnant patient with a preexisting illness.

ASTHMA

Asthma is one of the most common chronic medical problems in pregnancy, with a prevalence of between 3.7% and 9.4 %.[1] Maternal asthma is associated with an increased risk of preeclampsia or eclampsia, premature contractions, cesarean section, low birth weight, and small-for-gestational-age status.[1,2] The risk of such complications varies with the severity of the disease and degree of control during pregnancy. Adverse perinatal outcomes increase with the severity of asthma during pregnancy. Controlling asthma during pregnancy leads to less intrauterine growth retardation and fewer adverse perinatal outcomes.[1-3] It has been well documented that asthma may worsen, improve, or remain the same during pregnancy, but no studies have examined whether this is caused by changes in asthma treatment, severity, or sudden asthma attacks.[4]

Maternal respiratory function changes can make it more difficult to recognize the decompensating pregnant asthmatic patient. Tidal volume and minute ventilation increase by 45% over the course of pregnancy resulting in an average P_{CO_2} of 32 mm Hg. The kidneys compensate and maintain an average bicarbonate level of 19 mEq/mL, which results in a compensated respiratory alkalosis with a serum pH between 7.40 and 7.45.

Many adverse perinatal outcomes caused by asthma are thought to be due to fetal hypoxia. Thus, the overall goal of treatment is maintaining maternal oxygen saturations above 95%. Both the American College of Obstetrics and Gynecology (ACOG) and National Asthma Education and Prevention Program have clearly stated that it is safer to use asthma medications to treat pregnant women than to allow severe asthma symptoms and exacerbations to occur during pregnancy.

The standard treatment for a pregnant asthmatic patient is the same as that for a nonpregnant patient with an asthma exacerbation. After history and the performance of a physical examination, the peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV_1) should be measured. Patients with an FEV_1 or PEF less than 50% of their predicted maximum are classified as having a severe exacerbation. An initial fetal assessment should be performed, including fetal heart tones and continuous electronic fetal monitoring with a biophysical profile if the pregnancy has reached viability. Supplemental oxygen should be given to all mothers with oxygen saturation below 95%.

Inhaled short acting β_2-agonists are the first-line treatment for an asthma exacerbation and can be given continuously, if needed, for a severe exacerbation (Table 179.1). Long-acting selective β_2-agonists and inhaled corticosteroids, with budesonide being the preferred agent, can be added as controller medications on discharge from the ED. Multiple studies have shown no increased risk of adverse perinatal outcomes.[3-5] Nonselective β-agonists such as epinephrine are generally avoided because of concern for their effect on placental blood flow. It is important to note that β-agonists are tocolytics and will often halt labor.

Oral corticosteroids are indicated for use in moderate to severe asthma exacerbations and should be prescribed for the same indications as in nonpregnant asthmatics. Despite these recommendations, in multiple studies in the acute care setting, pregnant women with asthma exacerbations were between 17% and 21% less likely to be treated with oral corticosteroids than nonpregnant controls.[6,7] Reasons for this treatment disparity may be due to evidence that oral corticosteroid use increases the risk of preterm delivery and low-birth-weight infants; there is also conflicting evidence of an increased risk of orofacial clefts.[2-4] However the benefits of oral corticosteroid use for avoiding fetal hypoxia outweighs the risk of adverse perinatal outcomes.

Second-line agents for asthma control (eg, cromolyn sodium) are considered safe in pregnancy. In limited studies, magnesium has been shown to improve respiratory function in pregnant females with severe asthma exacerbations without adverse fetal outcomes.

CARDIOVASCULAR DISORDERS

Principles

Heart disease complicates more than 1% of pregnancies in the United States and leads to 20% of nonobstetric maternal deaths.[8-11] Hypertensive disorders are the most frequent cardiovascular events, occurring in 6% to 8% of pregnancies.[12] The

TABLE 179.1

Drugs Used to Treat Acute Asthma Exacerbations During Pregnancy

PHARMACOLOGIC CLASS	EXAMPLES	DOSAGE	COMMENTS
Inhaled beta agonists	Albuterol Levalbuterol	2.5–5 mg every 20 min 1.25–2.5 mg every 20 min	Inhaled beta agonists first-line therapy May also be administered by metered-dose inhaler; up to three doses in first hour; continuous use in severe exacerbations
Injectable beta agonists	Epinephrine Terbutaline	0.3–0.5 mg SC (1:1000 or 1 mg/mL) every 20 min 0.25 mg SC (1 mg/mL) every 20 min	No proven benefit over inhaled dosing; up to three doses in first hour
Systemic corticosteroids	Prednisone Prednisolone Methylprednisolone	Dosage applies to all preparations Initial inpatient therapy: variable dosing; need at least 120–180 mg/day Outpatient burst therapy—40–60 mg/day for 3–10 days	No benefit of intravenous dosing over oral except in patients with impending respiratory failure who cannot take oral medications
Inhaled anticholinergics	Ipratropium bromide	0.5 mg every 20 min	Not first-line therapy; should be used with beta agonists Consider for use in patients with severe exacerbations
Smooth muscle relaxants	Magnesium sulfate		Limited data on use for asthma in pregnancy

SC, Subcutaneous.

Adapted from National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program Asthma and Pregnancy Working Group: NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment—2004 update. J Allergy Clin Immunol 115:34–36, 2005.

proportion of maternal deaths due to cardiovascular disease has increased as pulmonary hypertension, cardiomyopathies, aortic dissection, and myocardial infarction have become leading causes of death.[11] The increase in blood volume due to pregnancy, along with the increases in preload, cardiac output, and oxygen consumption, can worsen or reveal cardiac disease in pregnant women. Because the signs and symptoms of acute coronary syndromes and heart failure (eg, shortness of breath, mild chest pain, edema) can be seen in normal pregnancies, these entities are especially difficult to diagnose.[10,12]

Chronic Hypertension and Hypertensive Emergencies

Hypertension commonly affects pregnant women, causing complications in 12% of pregnancies and 18% of maternal deaths in the United States. Chronic hypertension in pregnancy significantly increases the risk of superimposed preeclampsia, preterm delivery, intrauterine growth restriction, and cesarean section.[13] Chronic hypertension is defined as hypertension (>140 mm Hg systolic or >90 mm Hg diastolic) diagnosed prior to pregnancy or before 20 weeks' gestation (Table 179.2).

Many women have mild hypertension of pregnancy (defined as systolic blood pressure of 140–159 mm Hg or diastolic blood pressure of 90–109 mm Hg). Medical treatment of uncomplicated chronic hypertension in pregnancy without evidence of end-organ damage has demonstrated no benefit in reducing adverse perinatal outcomes as compared to placebo in multiple studies. Additionally, antihypertensive medications pose a risk of hypotension and decreased fetal blood flow.[14,15] Thus, the ACOG recommends that antihypertensive treatment should be started when blood pressures are consistently higher than 160 mm Hg systolic and/or higher than 105 mm Hg diastolic.[14] The major risk posed by severe chronic hypertension is a progression to preeclampsia, which occurs in 25% of these pregnancies. Antihypertensive drugs have proven to be effective in preventing this progression.[15]

The first-line oral agents for the treatment of chronic hypertension in pregnancy are listed in Table 179.3. The ACOG defines a hypertensive emergency as acute-onset persistent hypertension with systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 110 mm Hg. In these cases, parenteral therapy is indicated, with a target blood pressure range of 140 to 150 mm Hg systolic and 90 to 100 mm Hg diastolic, to prevent loss of cerebral autoregulation.[8,9] Therapy with intravenous (IV) labetalol is preferred, although hydralazine and oral nifedipine are also considered firs-line treatment (Table 179.4).[8,9,16] Although labetalol is recommended by the ACOG, it should be noted that regular beta blocker use during the first trimester has been associated with small-for-gestational-age newborns.[17]

In 2013, the ACOG changed its diagnostic criteria for preeclampsia to no longer requiring proteinuria. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in the presence of thrombocytopenia, impaired liver function, pulmonary edema, visual disturbances, and/or the development of renal insufficiency.[14]

Cardiac Disorders

Acute Coronary Syndromes

Pregnancy-related acute myocardial infarction (AMI) occurs in 6.2 of every 100,000 deliveries. The mortality rate in pregnant women who have had an AMI is from 5.1% to 7.2 %. Pregnant women are two to four times more likely to have an AMI as compared to age-matched nonpregnant individuals. As the number of women becoming pregnant who are older than 35 years increases, it is important to recognize that pregnant women aged 40 years or older have a 30-fold greater risk for acute coronary syndrome (ACS) than pregnant women 20 years of age or younger.[18] The incidence of AMI is highest during the last trimester and peripartum period.

Multiple factors are hypothesized to increase the risk of AMI in pregnancy, including a prothrombotic state, increased myocardial oxygen demand secondary to increased cardiac output and heart rate, and decreased oxygen-carrying capacity secondary to

Text continued on p. 2266

TABLE 179.2

Hypertensive Disorders of Pregnancy

	CHRONIC HYPERTENSION	GESTATIONAL HYPERTENSION	PREECLAMPSIA	CHRONIC HYPERTENSION WITH SUPERIMPOSED PREECLAMPSIA
Definition	Hypertension that antedates pregnancy[a]	Hypertension diagnosed after 20 wk of gestation in the absence of proteinuria or other evidence of preeclampsia	Hypertension that begins after 20 wk of gestation in association with new-onset proteinuria (>300 mg/24 hr) or symptoms below in the absence of proteinuria	Hypertension that antedates pregnancy in association with new-onset proteinuria
	Hypertension diagnosed before 20 wk of gestation		Decreased platelets, elevated liver transaminase levels, renal insufficiency, pulmonary edema	Sudden increase in proteinuria in woman with chronic hypertension[a] and proteinuria before 20 wk of gestation Hypertension that antedates pregnancy in association with sudden increase in blood pressure
	Comment—rarely, preeclampsia presents before 20 wk of gestation	Comment—may progress to preeclampsia; may also represent previously undiagnosed hypertension		Hypertension that antedates pregnancy in association with decreased platelets, elevated liver transaminase levels, renal insufficiency, pulmonary edema, or cerebral or visual symptoms

[a]Defined as blood pressure > 140 mm Hg systolic or > 90 mm Hg diastolic.
Adapted from Nishimura RA, Otto CM, Bonow RO, et al; ACC/AHA Task Force Members: 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129:e521–e643, 2010.

TABLE 179.3

Gestational Effects and Treatment of Medical Illnesses During Pregnancy

ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Asthma	Fetal—IUGR, PTD, hypoxia, meconium-stained amniotic fluid, fetal loss Maternal—preeclampsia, gestational hypertension, gestational diabetes, hyperemesis gravidarum, need for labor induction	Good prenatal outcomes seen in well-controlled asthma Treatment of acute exacerbations is the same as for the nonpregnant patient with the goal of keeping maternal oxygen saturations >95% to prevent fetal hypoxia. Fetal monitoring is recommended for exacerbations during the third trimester, even in the absence of maternal hypoxia. Maintenance therapy also is unchanged, with the following precautions: • Corticosteroids—inhaled agents preferred, but oral route may be necessary with acute exacerbations or severe, persistent disease; patients receiving long-term steroids require "stress dose" hydrocortisone during labor and delivery. • Methylxanthines—safe but debatable benefit; use only in refractory disease; reduced clearance during pregnancy may result in maternal toxicity and fetal tachycardia. • Leukotriene receptor antagonists—avoid zileuton.
Acute coronary syndrome	Fetal—perinatal death, PTD Maternal—uterine hemorrhage, abruption (related to use of antiplatelet, antithrombotic, fibrinolytic agents)	Standard medical therapy is the same as for the nonpregnant patient, although antiplatelet, antithrombotic, and fibrinolytic agents are best avoided when delivery is imminent. Avoid maternal hypotension when nitrates are used; they may result in fetal distress. Avoid beta blockers in the first trimester because they may cause fetal growth restriction. Coordinate definitive care (fibrinolytics vs. percutaneous coronary intervention) with cardiologist.

Continued

TABLE 179.3

Gestational Effects and Treatment of Medical Illnesses During Pregnancy—cont'd

ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Valvular heart disease	Fetal—perinatal death, PTD Maternal—heart failure, thromboembolism, death	Appropriate antithrombotic therapy is indicated for patients with prosthetic valves and atrial fibrillation (see text). Mitral stenosis—diuresis and beta blockade; avoid volume depletion when diuretics are used; valvuloplasty or open cardiac surgery for severe symptomatic disease; consider early pregnancy termination in women with severe stenosis. Mitral and aortic regurgitation—diuresis in patients with pulmonary congestion; surgical therapy for acute regurgitant lesions. Aortic stenosis—avoid hypotension and supine hypotensive syndrome; vigorous fluid replacement during delivery; valvuloplasty or open cardiac surgery for severe symptomatic disease; consider early pregnancy termination with severe symptoms despite therapy.
Hypertension	Fetal—perinatal death, IUGR, PTD Maternal—progression of target end-organ damage, superimposed preeclampsia, abruption, cardiac decompensation	Most perinatal complications occur in patients with preeclampsia or secondary causes of hypertension; outcomes are usually good with mild essential hypertension, and ACOG does not recommend treatment for blood pressures <160 mm Hg systolic or <10 mm Hg diastolic. The major risk posed by chronic hypertension in pregnancy is progression to preeclampsia, which occurs in 25% of these pregnancies. The most commonly used agents include methyldopa (preferred agent), labetalol, and hydralazine. Avoid beta blockers in the first trimester because they may cause fetal growth restriction and may also decrease placental blood flow. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers are teratogenic. Fetal cyanide poisoning might develop after several hours of sodium nitroprusside. Avoid prolonged infusions; use as agent of last resort.
Iron deficiency anemia	Fetal—low birth weight, PTD, low fetal iron stores, fetal loss (with severe anemia) Maternal—preeclampsia, high-output heart failure (rare); effects on maternal mortality unclear	Oral iron supplementation is indicated for patients with iron deficiency anemia. Recent evidence also supports prophylactic iron supplementation in pregnant patients. Several over-the-counter preparations are available. There is a delay from onset of therapy to an increase in the serum hemoglobin level. Parenteral iron replacement is safe and effective, although rarely required. Transfusion is rarely required but is a consideration for fetal well-being in mothers with severe anemia.
Sickle cell anemia	Fetal—fetal loss, IUGR, PTD, premature rupture of membranes Maternal—↑ need for cesarean section, preeclampsia, infection, heart failure, pulmonary infarction, ↑ incidence of painful crises; maternal mortality low with treatment; false-positive Apt and Kleihauer-Betke test results secondary to persistent hemoglobin F	Management of pain crises and infections is the same as for the nonpregnant patient, with rest, hydration, narcotic analgesia, supplemental oxygen, and antibiotics, as indicated. Narcotic analgesics should not be withheld, but the need for neonatal respiratory support should be anticipated if delivery is imminent. Prophylactic transfusion is not indicated. Fetal monitoring and assessment of fetal well-being are indicated for viable pregnancies. Chronic maintenance care includes pneumococcal vaccination and supplemental folate. Hydroxyurea has been discouraged during pregnancy, but few adverse fetal effects have been reported in humans.
Epilepsy	Fetal—various congenital malformations associated with AEMs, fetal hypoxia and bradycardia, fetal loss Maternal—variable changes in seizure frequency; alterations in AEM levels; increased seizure frequency secondary to voluntary medication noncompliance; abruption, anemia, hyperemesis gravidarum, preeclampsia, possible need for labor induction and cesarean section, premature rupture of membranes	Management of status epilepticus is the same as for the nonpregnant patient. Maintenance therapy should be coordinated by the patient's neurologist (or primary care practitioner) and obstetrician. In general, a single AEM given at the lowest effective dose is recommended. The newer AEM levetiracetam has demonstrated a lower incidence of birth defects and has equal to better efficacy as older AEMs. Folate supplementation (at least 0.4 mg/day) is indicated for patients taking AEMs. Consider administration of oral vitamin K to the mother during the last month of pregnancy and parenteral vitamin K to the newborn.

TABLE 179.3

Gestational Effects and Treatment of Medical Illnesses During Pregnancy—cont'd

ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Myasthenia gravis	Fetal—transient neonatal myasthenia syndrome Maternal—variable changes in disease severity; arrest of labor; disease exacerbation in postpartum period	Management is the same as for the nonpregnant patient. Ventilatory support is the most important aspect of therapy. Note that patients with myasthenia gravis are relatively resistant to depolarizing paralytic agents; higher doses may be required. Pyridostigmine therapy can be continued; intravenous therapy is recommended during labor. Patients receiving maintenance corticosteroids require "stress dose" hydrocortisone during labor and delivery. Plasmapheresis is safe during pregnancy.
Renal (chronic kidney disease)	Fetal—IUGR, low birth weight, polyhydramnios, fetal loss, increased NICU utilization, preterm birth Maternal—placental abruption, preeclampsia, increased need for cesarean section	Aggressive hypertension control Monitoring of proteinuria Treating worsening kidney dysfunction as if preeclampsia Beta blocker, calcium channel blocker, or hydralazine use with salt restriction Avoid ACE inhibitors.
Diabetes mellitus—insulin-dependent diabetes mellitus (IDDM), non–insulin-dependent diabetes mellitus (NIDDM), and gestational diabetes mellitus (GDM)	Fetal—congenital malformations; macrosomia; IUGR; fetal loss; neonatal hypoglycemia, jaundice, hypomagnesemia, and hypocalcemia Maternal—preeclampsia, "brittle" diabetes, ↑ need for cesarean section	Every attempt should be made to maintain maternal serum glucose concentration of 100 mg/dL; note that insulin requirements decrease during immediate postpartum period, the mother may not need insulin for 24–48 hr after delivery; insulin therapy, with intermittent dosing or continuous subcutaneous infusion, is standard care for patients with IDDM and NIDDM. Management of diabetic ketoacidosis is the same as for the nonpregnant patient, with the addition of an assessment of fetal well-being and continuous fetal heart monitoring; blood glucose concentration may be normal or only slightly elevated.
Obesity	Fetal—infant death, immune dysregulation and increased risk of neonatal asthma Maternal—excess gestational weight gain, increased risk of postterm delivery, failure to progress, preeclampsia, cesarean section, complications associated with cesarean section	Control of maternal gestational weight gain Monitoring for progression of gestation post-dates
Hyperthyroidism	Fetal—preterm birth, low birth weight, fetal thyroid dysfunction (leading to clinical picture of irritability, tachycardia, goiter, cardiomegaly, CHF, premature craniosynostosis, failure to thrive), fetal loss Maternal—preeclampsia, heart failure	Management of thyroid storm is the same as for the nonpregnant patient and includes a search for the underlying precipitant. Therapy for hyperthyroidism in the absence of thyroid storm: • Reversal of sympathetic effects— propranolol in standard doses is useful until thyroid hormone synthesis has been blocked by thioamides. • Thioamides—propylthiouracil (PTU) and methimazole at the lowest effective dose are acceptable; PTU is preferred. • Surgical therapy: thyroidectomy is useful in refractory cases. • Other—avoid iodide if possible; hydrocortisone decreases peripheral conversion of T_4 to the more active T_3 and can be used during pregnancy. Radioactive iodine is absolutely contraindicated.
Hypothyroidism	Fetal—congenital malformations, low birth weight, fetal loss, fetal thyroid dysfunction, and goiter Maternal—preeclampsia, abruption, postpartum hemorrhage, ↑ need for cesarean section	Maintenance therapy includes levothyroxine, 0.15 mg/day. Appropriate treatment prevents adverse obstetric and fetal outcomes. Myxedema coma is rare, but when present, treatment is the same as for the nonpregnant patient.

Continued

TABLE 179.3

Gestational Effects and Treatment of Medical Illnesses During Pregnancy—cont'd

ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Tuberculosis	Fetal—fetal loss, low birth weight, PTD; fetal and neonatal tuberculosis Maternal— preeclampsia; potential for delayed diagnosis and treatment out of concern for fetus	Positive response to purified protein derivative (PPD), normal chest radiograph—6- to 9-mo course of isoniazid (starting after the first trimester) for patients with recent conversion (<2 yr); patients who have been PPD-positive >2 yr may defer treatment until after delivery but should still be offered a course of isoniazid because it is safe in pregnancy. Increased index of suspicion in HIV-positive mothers with moderate to severe anemia. Active tuberculosis—9-mo course (starting immediately) of isoniazid plus rifampin or ethambutol (all three agents in combination recommended by American Thoracic Society). Multidrug-resistant tuberculosis warrants aggressive therapy, without regard to potential teratogenicity. Pyridoxine is indicated for all patients receiving isoniazid.
HIV/AIDS	Fetal—HIV infection, PTD, low birth weight, fetal loss; neonatal abstinence syndrome if mother uses injection drugs, teratogenicity associated with efavirenz (EFV) use Maternal—postpartum endometritis, uterine bleeding (in the setting of thrombocytopenia), progression of HIV disease in absence of HAART therapy	Antiretroviral therapy— • Highly active antiretroviral therapy (HAART) should be offered to all pregnant patients with HIV infection and viral load >1000 copies/mL. The HAART regimen should include zidovudine (AZT) to prevent vertical transmission of the virus. • There are specific HAART drug-related concerns during pregnancy; decisions about therapy are best made by appropriate specialists. • AZT monotherapy is not recommended except for those patients with a low viral load who do not wish to take HAART. In these cases, AZT is appropriate to reduce disease transmission. Cesarean section is recommended with viral load >1000 copies/mL. Opportunistic infections require standard therapies despite the potential fetal effects.
Syphilis	Fetal—congenital syphilis, fetal loss, PTD, IUGR, nonimmune hydrops	Primary, secondary, early latent (<1 yr)—benzathine penicillin G, 2.4 million units IM × one dose Late latent (>1 yr or unknown duration) — benzathine penicillin G, 2.4 million units IM weekly × three doses Neurosyphilis—aqueous penicillin G, 2–4 million units IV q4h × 10–14 days, or procaine penicillin G, 2.4 million units IM, and probenecid, 500 mg PO q6h × 10–14 days
Systemic lupus erythematosus (SLE)	Fetal— PTD, IUGR, fetal loss, cesarean section Maternal—SLE flare, worsening of renal dysfunction, thrombocytopenia, anemia, preeclampsia, subclinical coronary vascular disease	Initiation of aspirin therapy post–16 wk for decreasing preeclampsia risk. Close monitoring of SLE nephritis via decreasing C3 and C4 levels and elevated anti-DNA antibodies, monitoring of proteinuria. Markers of disease activity via increased lupus anticoagulant levels and antiphospholipid antibody levels Natural disease hiatus during pregnancy
Rheumatoid arthritis	Fetal—IUGR Maternal—increased flare within 1 yr of pregnancy	Aspirin after 16 wk EGA Azathioprine as a safer alternative to cyclophosphamide or methotrexate in first and second trimesters
Eating disorders (anorexia nervosa, bulimia nervosa [BN])	Fetal—miscarriage, low birth weight, preterm birth, congenital malformations (neural tube defects) Maternal—cesarean section, depression	Restoration of normal physiologic parameters (electrolyte replacement and clearance of ketosis) Antidepressants for BN
Alcohol	Fetal—IUGR, low birth weight, miscarriage, IUFD, fetal alcohol spectrum disorders Maternal—increased risk of unintended pregnancies, alcohol withdrawal	Any gravid patient with signs of active withdrawal should be considered for inpatient management.
Smoking	Fetal—miscarriage, IUFD, preterm birth, IUGR, SIDS, congenital deformities (clubfoot) Maternal—decreased risk of preeclampsia	Behavioral and cognitive treatment for cessation Nicotine patches in second and third trimesters appear safe in limited studies.
Opioids	Fetal—IUGR, SIDS, narcotic abstinence syndrome, NICU admissions Maternal—increased risk of unintended pregnancies, withdrawal, endocarditis	Close monitoring of fetal depression peripartum Management of methadone maintenance to decrease risk of IV drug injection complications

ACOG, American College of Obstetrics and Gynecology; *AEM,* antiepileptic medicine; *CHF,* congestive heart failure; *EGA,* estimated gestational age; *IUFD,* intrauterine fetal demise; *IUGR,* intrauterine growth restriction; *NICU,* neonatal intensive care unit; *PTD,* preterm delivery. *SIDS,* sudden infant death syndrome; T_3, triiodothyronine; T_4, thyroxine.

TABLE 179.4

Antihypertensive Agents for Hypertensive Emergencies

DRUG	ROUTE	STARTING DOSE	TITRATION DOSE	MAXIMUM DOSAGE	MODE OF ACTION	ONSET OF ACTION	DURATION OF ACTION	ADVERSE EFFECTS	COMORBID INDICATIONS
Hydralazine	IV (intermittent)	5 mg IV push or IM	5–10 mg IV every 20–40 min	30 mg	Direct smooth muscle relaxation	10 min	12 hr	Headaches, aggravation of angina, tachycardia, nausea, flushing, hypotension, lupus-like syndrome	Preeclampsia, eclampsia (first line)
Labetalol	IV (intermittent)	10–20 mg IV (over 2 min)	20–80 mg IV, every 20–30 min	300 mg	α_1-agonist + nonselective beta blockade	5–10 min	2–6 hr	Fetal, maternal bradycardia, heart block, postural hypotension, cold extremities, sleep disturbances, rebound hypertension, bronchospasm, masking of hypoglycemia	Preeclampsia, eclampsia (first line); acute pulmonary edema, diastolic dysfunction; acute myocardial infarction; hypertensive encephalopathy; aortic dissection; hypertensive encephalopathy; ischemic or hemorrhagic stroke
	IV (infusion)	1–2 mg/min	Increase by 1 mg/min every 10 min	300 mg					
Esmolol	IV (infusion)	Bolus—500 μg/kg Maintenance—50 μg/kg/min	Increase by 50 μg/kg/min every 4 min	300 μg/kg/min	Beta blockade	<1 min	15–30 min	First-degree heart block, maternal bradycardia, congestive heart failure, bronchospasm; crosses the placenta; may cause fetal bradycardia, persistent fetal beta blockade	Acute myocardial infarction; aortic dissection
Nifedipine[a]	Oral	10–20 mg	Repeat in 30 min if needed	30 mg	Calcium channel blocker	5–10 min	2–4 hr	Uncontrolled hypotension, stroke, myocardial infarction, flushing, headache, reflex tachycardia	
Nicardipine	IV (infusion)	5 mg/hr	Increase by 2.5 mg/hr every 5–15 min	15 mg/hr	Calcium channel blocker	1–5 min	4–6 hr	Tachycardia, flushing, and headache	Preeclampsia, eclampsia (first line); acute pulmonary edema, systolic dysfunction; hypertensive encephalopathy; acute renal failure; ischemic or hemorrhagic stroke
Sodium nitroprusside	IV (infusion)	0.25 μg/kg/min	Increase by 0.25–0.5 μg/kg/min every 2–3 min	5 μg/kg/min	Nonselective direct NO inhibitor	<1 min	2–3 min	Nausea, vomiting; potential risk for maternal and fetal cyanide and thiocyanate toxicity if used for >4 hr	Aortic dissection; acute pulmonary edema; left ventricular dysfunction

[a]Theoretical risks with simultaneous administration of magnesium (eg, severe hypotension, myocardial depression, potentiation or prolongation of neuromuscular blockage).
IM, Intramuscular; *IV,* intravenous; *NO,* nitrous oxide.
From Too GT, Hill JB. Hypertensive crisis during pregnancy and postpartum period. Semin Perinatol 37:280–287, 2013.

physiologic anemia, which may precipitate angina.[19,20] Hypertension, thrombophilia, anemia, diabetes, advanced maternal age, multiparous state, and smoking increase the risk of pregnancy-associated AMI.[19]

Approximately 13% to 25% of pregnant patients diagnosed with ACS have normal coronary arteries.[20] In one study, 43% of patients diagnosed with AMI had atherosclerosis, with or without thrombus, 21% had coronary thrombus, and 16% had dissection.[19] AMI with normal coronaries tends to occur during the peripartum period. Other causes such as coronary artery dissection and vasospasm are more likely to occur in otherwise normal vessels, whereas atherosclerotic disease causes most AMIs in the antepartum period. Pulmonary embolus, reflux esophagitis, biliary colic, and aortic dissection are all more common than myocardial ischemia during pregnancy and should be considered in the differential diagnosis of the pregnant patient who presents with chest pain. Initial signs and symptoms of AMI, such as chest pain and shortness of breath, are often attributed to the normal physiological changes of pregnancy.[18,20,21]

The diagnosis of ACS is similar to that in nonpregnant patients, with certain exceptions. Electrocardiographic changes sometimes occur in normal pregnancies and delivery. These include T wave flattening, T wave inversion (mainly in lead III), and nonspecific ST changes during pregnancy, as well as ST depression during labor induction for cesarean section.[20] As a result, an additional evaluation may be necessary. Echocardiography is useful in the correlation of suspicious electrocardiographic findings with wall motion abnormalities. The enzymatic diagnosis of myocardial infarction is unchanged, except during and immediately after delivery; the troponin level is preferred to the creatine kinase level because it rises above baseline during this time. The United Kingdom's Saving Mother's Lives Report has found that in gravid women who died from cardiac ischemia, care was substandard in 46% of cases. Key diagnostic and management issues include the following[21,22]:

- Ischemic cardiac disease as a cause of symptoms should be considered.
- Asymptomatic pregnant patients with ischemic cardiac disease may have a normal electrocardiogram (ECG), so evaluation for chest pain should include serial ECGs and troponin levels.
- A normal echocardiogram does not exclude myocardial infarction (non–ST segment elevation MI).
- Cardiologists are reluctant to perform coronary angiography because of pregnancy.

Treatment of AMI during pregnancy is similar in most respects to treatment of the nonpregnant patient, with survival of the mother as the goal (see Table 179.3). Standard treatments including antiplatelet agents, nitroglycerin, and beta blockers: antithrombotic agents are considered safe during pregnancy but the decision to use them should be made jointly by emergent consultation with a cardiologist.[18,21] Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, aldosterone antagonists, and statins are not advised until the postpartum period. Aspirin is the first-line antiplatelet agent. Clopidogrel and eptifibatide have been studied in case reports, with no adverse fetal outcomes, and the benefit of their use outweighs any risks.[21] Heparin has long been the antithrombotic of choice for pregnant patients, although low-molecular-weight agents such as enoxaparin also do not cross the placenta and are considered efficacious and safe in pregnancy.[18]

Cardiac catheterization with stenting is the treatment of choice for AMI in the pregnant patient and, with shielding, exposes the fetus to less than 1 radiation-absorbed dose (rad).[18] When a catheterization laboratory is unavailable, lifesaving thrombolytic therapy should not be withheld. Although thrombolytics do not cross the placenta, there is an increased risk of maternal hemorrhage and, in the setting of AMI caused by coronary dissection, thrombolytic use can worsen the dissection.[20,21] Because thrombolytic therapy precludes major surgery and epidural anesthesia in the hours to days immediately after administration, one must carefully consider whether to use these agents in pregnant women who are close to term, especially if the need for cesarean delivery is anticipated.

In the setting of peripartum AMI, labor should be conducted with continuous monitoring of the mother's hemodynamic status and fetal well-being. Assisted vaginal delivery is preferred unless there is an indication for cesarean section. Cesarean section avoids prolonged exertion by the mother but can subject the patient to general anesthesia if the use of antithrombotic agents precludes epidural catheter placement.

Valvular Heart Disease and Pulmonary Hypertension

Principles. The European Registry on Pregnancy and Heart Disease has reported that mitral stenosis and regurgitation are the most common types of valvular disease (63%), followed by aortic valve disease (23%).[23,24] The ability of patients to tolerate pregnancy without significant adverse effects depends on the type and severity of the lesion. Mild to moderate lesions (New York Heart Association [NYHA] classes I and II) are often associated with good outcomes for the mother and fetus. On the other hand, mitral stenosis (beyond class I), advanced aortic stenosis, and aortic and mitral lesions associated with moderate to severe ventricular dysfunction or pulmonary hypertension, as well as mechanical prosthetic valves requiring anticoagulation, can result in significant maternal mortality and require directed therapy and expert cardiology consultation (Table 179.5).[10,12,23,25]

Heart failure is the most common maternal complication in pregnancy with valvular heart disease.[23,24] In the European Registry on Pregnancy and Heart Disease, hospital admissions occurred in 38% of pregnant patients with valvular heart disease. Diagnosing heart failure is challenging because women in the last months of pregnancy experience symptoms such as dyspnea on exertion,

TABLE 179.5

Risk Classification in Women With Cardiac Disease[a]

LOW RISK	HIGH RISK
Aortic stenosis with ejection fraction >50% and mean gradient <25 mm Hg, asymptomatic	Severe aortic stenosis, regardless of symptoms
Aortic or mitral regurgitation, asymptomatic or mild symptoms	Aortic or mitral regurgitation, NYHA class III–IV
Mitral valve prolapse with mild or moderate regurgitation and ejection fraction >50%	Severe left ventricular dysfunction with ejection fraction <40%
Mild mitral stenosis without severe pulmonary hypertension	Symptomatic mitral stenosis, NYHA class II–IV
Mild to moderate pulmonary valve stenosis	Severe pulmonary hypertension (pulmonary artery pressure >75% of systemic pressure) Marfan syndrome Mechanical valve

[a]Maternal and fetal risk classification in women with cardiac valve disease according to the American College of Cardiology, American Heart Association, and European Society of Cardiology.

NYHA, New York Heart Association.

From Pessel C, Bonanno C: Valve disease in pregnancy. Semin Perinatol 38:273–284, 2014.

paroxysmal nocturnal dyspnea, orthopnea, and pedal edema that are identical to those of heart failure.[26] Normal B-type natriuretic peptide (BNP) levels can be used to rule out heart failure in pregnant females but, because BNP levels are higher in pregnant females, an elevated BNP level can be difficult to interpret.[27]

Pulmonary Hypertension. Pregnancy is poorly tolerated by patients with pulmonary hypertension because the pulmonary circulation cannot cope with the increased stroke volume and cardiac output of pregnancy, causing pulmonary pressures to rise. This causes dyspnea, heart failure, and syncope. Mortality in pregnant women with pulmonary hypertension has been reported to be as high as 50%, although a more recent study has demonstrated a mortality of 25% likely due to improvements in recognition and treatment.[28] Pregnancy is contraindicated, and patients early in pregnancy should be counseled about elective pregnancy termination.[29]

The treatment of the pregnant patient with pulmonary hypertension focuses on diuresis and pulmonary vasodilation. Diuretics are indicated for the management of volume overload, and common diuretics—with the exception of spironolactone—are considered safe, although limited data exist regarding their effect on the fetus.[29] Specific agents for treating pulmonary hypertension include endothelin receptor agonists (ERAs), phosphodiesterase inhibitors, and prostanoids. Phosphodiesterase inhibitors such as sildenafil and tadalafil, as well the prostacyclin derivatives epoprostenol and treprostinil, have not been shown to be fetotoxic in animals and are regularly used in pregnancy. ERAs such as bosentan and ambrisentan are teratogenic.

Mitral Stenosis. Mitral stenosis is the most commonly encountered valvular lesion in pregnancy and is also the most important lesion to detect in early pregnancy because it can cause maternal mortality.[10,12,23] The increased resting heart rate and stroke volume in normal pregnancy increase the pressure gradient across the mitral valve and can cause symptoms of left heart failure, as well as atrial arrhythmias such as atrial fibrillation.[10] The likelihood of maternal symptoms and worsening of cardiovascular status is directly related to the severity of disease. Pregnancy in women with mild mitral stenosis is generally well tolerated.

Beta blockers are the mainstay of treatment for patients with symptomatic mitral stenosis. Diuretics may also be used for patients with symptoms of heart failure[10,12,23,25] (see Table 179.3). Surgical intervention is indicated for patients with refractory symptoms despite optimal medical management and in patients with pulmonary hypertension.[12,25]

Aortic and Mitral Regurgitation. Mitral valve prolapse is the most common cause of mitral regurgitation in developed countries, whereas rheumatic heart disease is the most common cause worldwide.[23] In most cases, chronic regurgitation lesions are well tolerated during pregnancy and may even improve because the reduced systemic vascular resistance of pregnancy allows more forward and less regurgitant flow. In addition, this effect is aided by the increase in heart rate and shortened diastole that occur in pregnancy.[23] When necessary, medical therapy consists of diuresis, digoxin, and vasodilators.

Aortic Stenosis. Symptomatic aortic stenosis during pregnancy usually occurs in the setting of a congenital bicuspid valve. Patients with mild to moderate aortic stenosis tend to have uncomplicated pregnancies; conservative management is often possible, especially if the aortic valve area is greater than 1.0 cm^2. Patients with symptomatic aortic stenosis may respond to bed rest or preload reduction with diuretics. Severely symptomatic patients may need percutaneous valvotomy and surgical replacement.[23,24]

Prosthetic Heart Valves. Pregnancy is a hypercoagulable state and leads to an increased risk of thromboembolic events, especially in patients with prosthetic valves or underlying valvular disease.[23,24] Pregnant patients with prosthetic heart valves who are not anticoagulated have a maternal mortality as high as 5%, and thromboembolic events can occur in up to 24% of cases.[25] Warfarin is the most effective anticoagulant in preventing maternal thromboembolic events.[12] However, warfarin is considered teratogenic in the first trimester. Neither unfractionated heparin (UFH) nor low-molecular-weight heparin (LMWH) crosses the placenta and are not teratogenic. However, their use throughout pregnancy is not recommended due to the increased risk of thromboembolic events as compared to using UFH or LMWH in the first trimester, followed by warfarin for the remainder of pregnancy.[12,25]

Current anticoagulation recommendations in pregnant patients with prosthetic heart valves are to continue using warfarin until pregnancy has been achieved. If an international normalized ratio of 2.5 to 3.5 can be achieved with a warfarin dose less than or equal to 5 mg, warfarin may be used throughout pregnancy after a full discussion with the patient about the benefits and risks of the therapy. If a dose more than 5 mg is required, UFH or LWMH should be used in the first trimester, with warfarin being resumed for the second and third trimesters.[12,25] Warfarin should again be replaced by UFH or LWMH several weeks before delivery.

HEMATOLOGIC DISORDERS

Anemia

Anemia is the most common medical complication of pregnancy. Recent research has indicated that anemia may be associated with maternal mortality, perinatal mortality, preterm birth, low birth weight, and small-for-gestational-age infants.[30] The classic clinical presentations of anemia include pallor, fatigue, and shortness of breath.[31] Most anemia, however, is asymptomatic. The hemoglobin threshold for severe anemia requiring blood transfusions is typically considered to be less than 7 g/dL for gravid patients and less than 8 g/dL for postpartum patients.[31] There are several types of anemia exist, but four types predominate: dilutional anemia, iron deficiency, folate deficiency, and sickle cell hemoglobinopathy.

Dilutional Anemia

Dilutional anemia differs slightly from the other three. Where iron deficiency, folate deficiency and sickle cell hemoglobinopathy anemias are complications of pregnancy, dilutional anemia is a normal process associated with pregnancy. In preparation for blood loss at delivery, blood volume increases by nearly 50% between weeks 6 and 34. This rapid blood volume increase, accompanied by a lag in red blood cell (RBC) production, results in a dilution of hemoglobin. The result is that the threshold for anemia in gravid patients is slightly lower (11 g/dL) than in nongravid patients (12 g/dL). Pregnant patients with hemoglobin values typically considered normal in the nongravid patient have an increase in adverse outcomes such as preeclampsia, intrauterine growth retardation, and preterm birth, and the emergency clinician should consider that gravid patients with hemoglobin values of 13 to 15 g/dL have inadequate expansion of their plasma volume.[32]

Iron Deficiency Anemia

Iron deficiency anemia is common, occurring in approximately 20% to 25% of pregnancies in industrialized countries.[33] The risks of adverse pregnancy outcomes (see Table 179.3) have been noted

to relate to the severity of the anemia. Studies have indicated a higher risk of preterm birth and low birth weight in patients with mild to moderate anemia,[30,34] whereas severe anemia (<6 to 7 g/dL or 60–70 g/L) is associated with increased fetal mortality, abnormal fetal oxygenation, premature rupture of membranes, gestational hypertension, and reduced volume of amniotic fluid.[35] The diagnosis is made most accurately in the very early stages of pregnancy because serum ferritin, the most sensitive and specific (and preferred) test, is affected by the dilution effect of increased plasma volume occurring later in pregnancy. Other supporting laboratory evidence includes low plasma iron levels, increased free erythrocyte protoporphyrin, and elevated total iron-binding capacity.

The ACOG has developed guidelines for the management of iron deficiency anemia. Patients with an uncomplicated physiologic anemia who are not iron-deficient can be expected to have good obstetric outcomes without therapy and do not require treatment. Patients presenting with iron deficiency anemia should be treated with non–enteric-coated supplemental iron. The use of prophylactic supplementation in women with normal hemoglobin levels (>11 g/dL [110 g/L]) and normal iron stores (ferritin > 20 mg/dL [20 µg/L]) to prevent anemia in late pregnancy is controversial. However, recent studies and meta-analyses have demonstrated that prenatal iron supplementation significantly reduces the risk of anemia at term by 70% and the risk of iron deficiency anemia at term by 57% to 66%.[36-39] The dose of iron recommended by the World Health Organization (WHO) is 60 mg/day, but the Institute of Medicine has suggested an upper limit of 45 mg/day due to the gastrointestinal side effects of higher doses.

Folate Deficiency

Folate is critical to several intracellular processes associated with cell growth. However, due to the 5- to 10-fold increase in folate requirements during pregnancy, gravid patients are at risk for folate deficiency.[40] Folate deficiency is one of a number of causes of megaloblastic anemia, which is the second most common anemia.[41] The incidence of folate deficiency in pregnancy is low in developed countries but remains higher in other populations. The risk for development of folate deficiency is increased in patients with multiple gestations, short interpregnancy intervals, preexisting malnutrition, hyperemesis gravidarum, malabsorption syndromes, alcoholism, use of certain antiepileptic drugs, and diets lacking green leafy vegetables and animal protein. Low maternal folate stores have, most importantly, been linked to increased risk of neural tube defects, as well as increased risk of placental abruption, preterm birth and low birth weight, preeclampsia, and spontaneous abortion.[41,42] As is the case for iron deficiency, effects on the fetus depend on the degree of anemia.

Iron deficiency and folate deficiency anemias often coexist, making the peripheral blood smear difficult to interpret. In cases of suspected folate deficiency, the measurement of serum and RBC folate levels is indicated. However, the serum folate level is noted to exhibit a rapid response to folate intake, and low levels may normalize within days after a folate-rich meal. The serum folate level is also affected by the hemodilution of pregnancy. Oral folate supplementation with 0.4 mg daily is routinely recommended for all women before conception, and 0.4 to 0.8 mg is recommended during pregnancy as the requirement for this micronutrient increases during gestation. The ACOG recommends 1.0 mg for those women who have a known pregnancy-related folate deficiency.[21] Women at higher risk for neural tube defects (eg, neural tube defects in prior pregnancy) are advised to take much higher doses of folate, 4 mg daily, under close supervision of their obstetrician.[43] ACOG advises continuing oral folate supplementation throughout the second and third trimesters.[41]

Sickle Cell Anemia

Sickle cell disease (SCD) is one of the major sources of maternal and fetal complications in the United States. The details of the pathophysiologic mechanism and genetics of SCD are discussed in Chapter 112, but it is useful to review the most common phenotypes that affect pregnancy. The sickle gene can be homozygous (hemoglobin *SS* or *SCD*), and this form of the disease is responsible for most pregnancy complications. The sickle gene can also be heterozygous with normal hemoglobin A (sickle cell trait, or hemoglobin SA), in which case symptoms are rare, except under extreme environmental conditions. Hemoglobin S can also be heterozygous with a large number of abnormal hemoglobins, such as hemoglobin C, several variants of thalassemia, and other rare hemoglobin variants; each variant has its own complication profile. Of these, the most relevant in terms of pregnancy complications is hemoglobin SC.

Patients with SCD are subject to many chronic medical problems secondary to a variety of pathophysiologic mechanisms, including sickling of RBCs, anemia, immunosuppression caused by autosplenectomy, and repeated transfusion. Median life expectancy is in the fifth decade for both genders affected by SCD, and female fertility is generally unaffected, so it is likely that the emergency clinician will encounter pregnant patients with the disease. Maternal complications are common in patients with SCD; these include preterm labor, eclampsia, premature rupture of membranes, maternal infections, more frequent pain crises, thrombosis, preeclampsia, and increased need for cesarean delivery.[44-46] Despite these complications, the maternal mortality rate is less than 1% with current treatment.

SCD also results in adverse effects on the fetus (see Table 179.3). Placental infarction and insufficiency are common, and the incidence of premature labor, small-for-gestational-age infants, and low-birth-weight infants is significantly increased in SCD pregnancies compared with normal controls. The reported perinatal mortality rate varies but is low in the setting of appropriate maternal and neonatal care.[44-46]

Vasoocclusive crises and anemia occur more often in pregnancy and are the most common complications of SCD in pregnancy.[45,47] There have been no good randomized trials studying the management of SCD during pregnancy, so recommended treatment is similar to that for the nonpregnant patient (see Table 179.3). Hydroxyurea is not recommended for use in pregnancy because of potential teratogenicity, and nonsteroidal antiinflammatory drugs (NSAIDs) are avoided after 30 weeks of gestation. General anesthesia can result in an increase in postpartum sickling complications, so regional anesthesia is preferred in the case of cesarean delivery. The use of supplemental iron and transfusion is controversial because of the potential for iron overload, alloimmunization, volume overload, and hyperviscosity syndrome. Therapeutic transfusions should be given to patients with severe disease manifestations such as symptomatic anemia, cardiopulmonary instability, acute chest syndrome, intrapartum hemorrhage, and preeclampsia.[45,46,48] In general, the goal with transfusion or exchange transfusion is to lower the percentage of hemoglobin S to 40% and achieve hemoglobin values of approximately 10 g/dL (110 g/L). Transfusions aimed solely at secondary prevention of adverse events such as pain crises have not shown improvement in pregnancy outcomes.[45,47,48]

NEUROLOGIC DISORDERS

Epilepsy

Epilepsy is the most common neurologic complication of pregnancy but remains relatively rare, affecting less than 1% of all

gestations. Epilepsy refers to a broad spectrum of seizure disorders that range from relatively benign and infrequent seizures to a disabling condition with daily, poorly controlled generalized convulsions; therefore, care is individualized. The treatment of epilepsy during pregnancy entails balancing the risk of increased frequency and duration of seizures to the mother and fetus against the teratogenic risks of antiepileptic drugs (AEDs).

The effect of pregnancy on epilepsy is variable. Most epileptic patients (50%–76%) experience no change in their seizure frequency, whereas approximately 15% experience more frequent seizures.[49] Delivery and the first 24 hours postpartum are the most likely times for a seizure to occur, with a ninefold greater incidence of seizure than during pregnancy in general. A decrease in plasma drug concentrations is expected with certain AEDs, such as phenytoin, lamotrigine, oxcarbazepine, and levetiracetam.[50] Many authors have recommended that maternal plasma drug levels should be monitored and compared to prepregnancy levels.[49,50] Antiepileptic medications also increase the clearance of medications, including oral contraceptives, making unintentional pregnancy a possibility.

Gravid patients with epilepsy may be at increased risk for cesarean section, postpartum hemorrhage, and other adverse outcomes (see Table 179.3).[33] Patients who have nonconvulsive seizure disorders or who are seizure-free for a sufficient period of time before conception are candidates for nonpharmacologic observation because the risk of treatment with AEDs can outweigh the benefit.[49] This decision should be deferred to the patient's primary physician or neurologist. However, there are significant obstetric complications related to prolonged seizure activity, and long-term treatment with an AED for most patients with seizures is warranted (see Table 179.3).

The primary complication of AED use in pregnancy is congenital malformations. Of primary concern is the risk for neural tube defects, facial clefts, cardiac anomalies, and cognitive defects with the older generation agents (eg, valproate, carbamazepine, phenytoin) and the newer generation agents (eg, lamotrigine, topiramate, levetiracetam). There is a two- to three-fold increase in the incidence of serious congenital malformations in offspring of epileptic mothers taking these agents. The risk is greatest with valproate and is also increased with AED polypharmacy and increased dose of individual agents.[50,51-53] Of all the older agents, carbamazepine appears to be the safest for use as monotherapy.[50,53] Recent studies have looked at the risk of major congenital malformations of the newer AEDs and have found that in monotherapy with lamotrigine or levetiracetam, the risks are lower than those in the older agents.[49,51,52] Specifically, the United Kingdom and Ireland Epilepsy and Pregnancy Registry has found a rate of major congenital malformations of 0.7% for women receiving levetiracetam monotherapy; the North American AED Pregnancy Registry found a rate of 2.4%.[52,54] Both these rates are significantly below those of other AEDs.

When compared to the older AEDs, levetiracetam performed as well at controlling seizures when used in monotherapy. However, lamotrigine and topiramate, when used in monotherapy, showed worse seizure control.[55] Because phenytoin, carbamazepine, valproate, and possibly other AEDs interfere with folate metabolism, oral supplementation with at least 0.4 mg/day is recommended for all women of childbearing age taking these drugs to help prevent congenital malformations such as neural tube defects. Enzyme-inducing AEDs such as carbamazepine, phenytoin, and phenobarbital have been reported to cause neonatal vitamin K deficiency and neonatal hemorrhage, but the American Academy of Neurology and American Epilepsy Society have noted that there is inadequate evidence to determine a definitive relationship.

Any potential cause of seizure, including eclampsia, may result in status epilepticus. Despite this, status epilepticus in pregnancy is relatively rare, and limited data are available about its occurrence and therapy. Observations from the European Epilepsy Pregnancy Registry have noted that status epilepticus may occur at any time during gestation and even at delivery. It may also occur in patients who have been seizure-free throughout pregnancy, and no specific risk factors for its occurrence have been identified. Older reports noted a high fetal and maternal mortality, but recent data support a much lower complication rate.

The risk of untreated status epilepticus to the mother and fetus clearly outweighs the potential for adverse teratogenic effects, and standard resuscitative measures, as well as drug therapy, are indicated. Continuous fetal monitoring should be instituted as soon as possible to observe for signs of fetal hypoxia, and the mother should be positioned in the left lateral decubitus position to avoid the supine hypotensive syndrome.[49]

Multiple Sclerosis

Multiple sclerosis (MS) affects approximately 400,000 Americans and is twice as common in women as in men. The peak age at onset is 20 to 35 years, which overlaps peak childbearing years. The disease is characterized by intermittent episodes of central nervous system (CNS) demyelination, with consequent neurologic impairment that follows a relapsing-remitting course. Progressive neurologic deficits and permanent disability develop in certain patients.

The impact of pregnancy on the course of MS has been closely studied in various cohorts and, as in other autoimmune diseases, the frequency and severity of exacerbations of MS improve because of the immunosuppressant effects of pregnancy. This effect is most pronounced in the third trimester. During the 3 months after delivery, the rate of relapse increases and then returns to the prepregnancy baseline.[56,57] Relapses are more likely in MS patients with higher disability at the time of pregnancy onset. However, it does not seem that postpartum relapses are related to the duration of disease or total number of relapses before conception.[56,57]

MS patients with disease exacerbation are often treated with immunomodulators such as intravenous immune globulin (IVIG), corticosteroids, glatiramer acetate, and interferon beta. Small studies in gravid patients have shown that the use of IVIG during pregnancy and in the postpartum period is safe and may decrease the relapse rate.[57] Likewise, the use of intermittent steroids in the postpartum period may decrease the likelihood of disease relapse. Although the evidence is not conclusive, it is currently not recommended to treat MS exacerbations during pregnancy with interferon beta or glatiramer acetate based on evidence that they may cause adverse fetal effects.[58,59]

Spinal Cord Injury

Because spinal cord injury (SCI) occurs mainly in young people and usually does not impair fertility, there is a relatively large population of paraplegic and quadriplegic patients who become pregnant.[60] Pregnant women with SCI are twice as likely to have preterm labor and are at increased risk of having a low-birthweight infant.[61] Although many of these pregnancies are uneventful, these patients are at risk for certain complications.

The hypercoagulable state of pregnancy, combined with chronic immobilization, results in an increased incidence of thromboembolic disease, with the incidence of deep vein thrombosis (DVT) reported as high as 8% in pregnant women with SCI.[60] The incidence of urinary tract infection is also markedly increased as a result of neurogenic complications and the need for catheterization.[60] Infections are even more likely during pregnancy and may progress to pyelonephritis, with the subsequent increased risk of fetal loss, prematurity, and maternal sepsis.

Autonomic dysreflexia is the most serious complication of SCI and occurs in up to 85% of women with high lesions (above T5-T6); it occurs with increased frequency during pregnancy.[60] Autonomic dysreflexia is manifested as severe paroxysmal hypertension, headache, tachycardia, diaphoresis, piloerection, mydriasis, and nasal congestion. It is often precipitated by afferent stimuli from the hollow viscus such as the bladder, bowel, or uterus. Symptoms of autonomic dysreflexia often occur with uterine contractions during labor. However, labor may be difficult to detect because patients with spinal cord lesions below T10 to T12 have an intact uterine nerve supply and will experience labor pains; however, with lesions above T10, labor may be imperceptible or experienced as only mild abdominal discomfort. Pregnant patients with SCI with symptoms of autonomic dysreflexia should be assessed for cervical dilation and have uterine contractions monitored. ED treatment is directed at the restoration of normal blood pressure with standard agents. Definitive therapy is with regional anesthesia. Spinal anesthesia and epidural anesthesia obliterate and prevent this response and should be used as soon as possible during labor for all women with SCI. Finally, it can be difficult to differentiate between the symptoms of autonomic dysreflexia and preeclampsia. In autonomic dysreflexia, symptoms such as hypertension will resolve once the stimuli to the skin or hollow viscus have been relieved; in preeclampsia, the symptoms and laboratory abnormalities are more likely to persist.[60]

Myasthenia Gravis

Myasthenia gravis is a rare disorder in which autoimmune destruction of the postsynaptic cholinergic receptor results in profound muscle fatigability. The effect of pregnancy and postpartum state on myasthenia gravis is unpredictable in the individual patient, but overall, approximately 25% to 40% of patients experience exacerbation of disease, with the remainder having improvement or no change in disease severity.[62-64] Disease exacerbations are most likely in the first trimester or puerperium, with improvement in symptoms often seen in the second and third trimesters due to the hormone-mediated immunosuppression of pregnancy.[63] Because of weight gain, anemia, and other physiologic adjustments of pregnancy that may result in fatigue, the distinction between normal pregnancy symptoms and myasthenia may be difficult. Also, these changes, along with the nausea and vomiting of normal pregnancy, may result in a need to adjust medication dosage requirements.[63]

Most deliveries are accomplished vaginally without complication in adequately treated patients; assisted and surgical delivery in these women is indicated mainly for obstetric reasons rather than for specific myasthenia-related care.[62] Up to 30% of neonates born to mothers with myasthenia gravis have a transient neonatal myasthenia syndrome through the placental transport of acetylcholine receptor antibodies.[63,64] There is no correlation between the severity of maternal disease and occurrence of neonatal myasthenia.[63] The onset of neonatal myasthenia is typically within the first hours of life but may be delayed by a period of days. Manifestations include poor feeding and suck, diminished reflexes, hypotonia, and bulbar and respiratory muscle weakness. As in adults, the symptoms respond to cholinesterase inhibitors, but treatment should be carried out in an intensive care unit setting.[64]

Myasthenia crises during pregnancy present with typical symptoms of painless fluctuating weakness of skeletal muscles. With extraocular muscle involvement, diplopia and ptosis are the most common early symptoms.[63] When exacerbations do occur, treatment is no different from the treatment of nonpregnant patients (see Table 179.3). Acetylcholine esterase inhibitors, corticosteroids, azathioprine, IVIG, and plasmapheresis are all considered safe for the mother and fetus.[64] Assessment of pulse oximetry, forced vital capacity, and arterial blood gas parameters will guide respiratory therapy. For patients presenting with weakness, an edrophonium (Tensilon) challenge test to distinguish myasthenia from cholinergic crisis is appropriate after the initiation of appropriate ventilatory support. Standard medical treatment is continued during labor and delivery to maximize motor strength. Epidural anesthesia is also recommended to reduce pain and fatigue. The emergency clinician should be aware that 30% of patients experience an exacerbation during the postpartum period as the protective immunosuppressant effect of pregnancy dissipates.[63,64]

RENAL DISORDERS

Chronic kidney disease (CKD) can be silent well into its disease course and is more difficult to diagnose in pregnancy because of expected decreased blood urea nitrogen (BUN) and creatinine levels during pregnancy. For women with known renal disease, including end-stage renal disease, on hemodialysis, pregnancy rates are 1% to 7%. For those post–renal transplantation, fertility rates return to prerenal failure levels within 1 to 6 months post-transplantation, so pregnancy is not an uncommon finding in posttransplantation women of childbearing age.

CKD in and of itself is an independent risk factor for maternal and fetal complications. The degree of underlying renal dysfunction is a strong determinant of morbidity associated with pregnancy. Patients with moderate to severe renal dysfunction have a much higher risk of further decline in renal function, as well as adverse obstetric outcomes, including preeclampsia, placental abruption, fetal loss, preterm delivery, low birth weight, polyhydramnios, and increased need for cesarean section and neonatal intensive care.[65,66] Despite this, 80% of pregnancies with a maternal BUN level higher than 60 mg/dL ended in the delivery of live births. Worsening of underlying renal function is more likely in patients with a decreased glomerular filtration rate who also have associated proteinuria or hypertension. Because worsening renal function is manifested by hypertension and proteinuria, differentiation from preeclampsia can be difficult. In this setting, it is best to treat the patient for presumed preeclampsia, with the caveat that magnesium administration should be performed judiciously on the basis of serum magnesium levels.

Pregnant women with chronic renal failure require aggressive and timely management to optimize their chances for a successful gestation without causing further deterioration in renal function. One of the most successful tenets of CKD management in pregnancy is close control of blood pressure and monitoring for proteinuria. Treatment regimens are the same as those outlined earlier (see "Chronic Hypertension and Hypertensive Emergencies").

Evidence of renal function deterioration or the development or exacerbation of hypertension warrants admission for specialized inpatient care. Hemodialysis is indicated for creatinine levels above 3.5 to 5 mg/dL (266.9–381.3 μmol/L). Pregnancy in women who are already dialysis- dependent has been associated with poor outcomes, and pregnancy has previously been discouraged in these patients. However, studies including small numbers of women have noted live birth rates approaching 60% to 85% when mothers receive specialized prenatal care.[65,66] Such care includes correction of anemia, appropriate antihypertensive therapy, and more aggressive dialysis with more frequent or prolonged sessions.[66]

METABOLIC AND ENDOCRINE DISORDERS

Diabetes

Three types of diabetes affect pregnant patients—type 1, or insulin-dependent diabetes mellitus (IDDM); type 2, or

non–insulin-dependent diabetes mellitus (NIDDM); and gestational diabetes mellitus (GDM). Although risk factors for GDM can be identified prepregnancy, it is not classified as a preexisting medical condition and will not be considered in this discussion. However, the considerations for glycemic control in GDM are the same as those for IDDM and NIDDM. Although NIDDM is sometimes considered a more benign form of disease, the risk of pregnancy complications and fetal malformations is, at best, the same for NIDDM and IDDM. Some studies have shown that complications, maternal and fetal, are actually greater for NIDDM.[67]

This represents a distinct medical challenge, given the ever-increasing prevalence of NIDDM and the generally lower rates of glycemic control and preconception planning in this patient population. In general, maternal and fetal complications relate to inadequate glycemic control and to the presence of vascular complications or severe renal insufficiency more than to the type of diabetes. Glycemic control is incrementally more challenging during pregnancy because of complexities in glucose regulation precipitated by hormonal changes. Specifically, in early pregnancy and again in the peripartum period, hyperglycemia is common and is caused by increased insulin resistance, even in IDDM patients. Obesity and preexisting insulin resistance in NIDDM can further complicate efforts of glucose control.[68] Ideally, hemoglobin A_{1c} (HbA_{1c}) values should not be higher than 6% (see Table 179.3); the best outcomes occur when tight glycemic control is achieved for at least 4 months preconception.[69] Experts have recommended that NIDDM patients taking oral agents be transitioned to insulin during pregnancy.[69] The predisposition to develop diabetic ketoacidosis (DKA) throughout pregnancy has been well documented; this is attributable to hormonal changes. An increased risk of significant hypoglycemic episodes stems from attempts at very tight glucose regulation, but is also caused by diminished glucagon response to hypoglycemia, emesis, and increased metabolic demands of the placenta and growing fetus.

Maternal Complications

The effects of pregnancy on underlying diabetes vary by organ system. The data are limited, but pregnancy is not advised for diabetic patients with significant coronary artery disease because of the cardiovascular demands of pregnancy and high mortality of AMI during pregnancy. Given the likelihood of silent ischemic events in the diabetic population, atypical or vague presentations of angina or MI, including new-onset congestive heart failure should be carefully evaluated in those with preexisting known coronary artery disease, but also in any diabetic mother.[70]

Patients with diabetic nephropathy are at increased risk for preeclampsia and the subsequent requirement for preterm delivery. Following progression of nephropathy closely in conjunction with aggressive blood pressure control and optimizing protein intake are strongly recommended.

Retinopathy worsens acutely in 77% of pregnancies, and those at greatest risk for this are patients with high HbA_{1c} levels, hypertension, nephropathy, and active nonproliferative or proliferative retinopathy. Laser therapy of preexisting retinopathy is recommended before conception, as well as for pregnant patients with severe disease.[71-73] Patients with known proliferative retinopathy should be counseled to avoid excessive, aggressive Valsalva maneuvers during labor to minimize the risk of retinal hemorrhages.[70]

Autonomic neuropathy does not accelerate during pregnancy, with the exception of a possible increase in symptomatic severity of gastroparesis.

DKA occurs in up to 9% of diabetic patients during pregnancy and may be the initial presentation of diabetes. DKA is usually seen in patients with IDDM but also complicates pregnancies in women with NIDDM and GDM. Common precipitating events include the typical factors seen in nonpregnant patients, such as insulin noncompliance and infection. Other pregnancy-specific factors are increased insulin resistance, hyperemesis, use of beta-mimetic medications for tocolysis, and use of corticosteroids to hasten fetal lung maturity. The serum pH may be deceptively normal in a pregnant patient with DKA because the initial pH tends to be higher in pregnancy as a result of physiologic hyperventilation. In addition, the serum glucose concentration may be normal or only moderately elevated. Therefore, screening for DKA is indicated in gravid diabetics with nausea, vomiting, malaise, or headache or in those with persistent hyperglycemia. Maternal mortality is rare in those with appropriately treated DKA. Fetal mortality rates are relatively high, ranging from 10% to 35%.[74]

Fetal Complications

Diabetes has many deleterious effects on the fetus (see Table 179.1). The risk of congenital anomalies in infants of diabetic mothers (IDMs) is as high as 10%.[74] The rate of congenital malformations in patients with prepregnancy diabetes is increased threefold or fourfold compared with the nondiabetic population, with anomalies being more likely in pregnant women with poor glycemic control.[69,74,75] Macrosomia is the most likely factor leading to the need for cesarean section and has been associated with shoulder dystocia. Conversely, preeclampsia and placental infarction secondary to vascular disease may result in impaired fetal development and stillbirth.[76] Diabetic patients are also at increased risk of spontaneous preterm delivery and labor-induced preterm deliveries.[76] Neonatal complications seen at increased rates in IDMs include transient tachypnea of the newborn, neonatal hypoglycemia, hypocalcemia in the peripartum period, hyperbilirubinemia, polycythemia, cardiomyopathy, and respiratory distress as a result of fetal hyperinsulinemia.

Management

Early management of diabetes in pregnancy in the ED requires the careful management of hyperglycemia or hypoglycemia because congenital abnormalities can occur in the first trimester. Treatment of NIDDM and IDDM requires individualized and carefully adjusted insulin administration, with the goal of maintaining strict glycemic control while avoiding hypoglycemia.

Treatment of DKA in pregnancy generally follows the same principles as those in nonpregnant patients, except that fluid resuscitation and insulin therapy should be maintained in the presence of normoglycemia until bicarbonate levels return to normal, indicating that any lagging acidemia has cleared. Fetal viability and well-being should be assessed in all cases of maternal DKA.

The timing and mode of delivery depend on whether obstetric or maternal complications exist. In the absence of suspected problems, vaginal delivery at term is recommended. Elective delivery is indicated in the setting of poor metabolic control, significant diabetic complications, and fetal macrosomia with suspected birth weight more than 4500 g.[75]

OBESITY

It is well documented that the incidence of obesity is increasing.[77] Obesity has been found to be an independent risk factor for poor predictors of pregnancy outcome, even without the comorbid conditions of diabetes, vascular disease, or hypertension.[78] Maternal risks include an increased incidence of gestational weight gain and increased risk of postterm delivery, preeclampsia, and inadequate contraction patterns in labor, leading to failure to progress. This is thought to be caused by an independent influence of obesity on myometrial activity.[79] The increased risk of undergoing

cesarean section is 3.2-fold of that seen in the nonobese population,[80] and postsurgical complications of hematoma, seroma, abscess formation, and wound dehiscence all increase in obese postpartum, cesarean section mothers.[81] Meta-analysis has shown obesity to be an independent risk factor for infant death and neonatal asthma; this risk is proportional to increased body mass index (BMI).[82] Obesity has not been associated with increased rates of shoulder dystocia, congenital malformations, or low 5-minute Apgar scores, however.[78,80] The BMI does not appear to be correlated with postpartum hemorrhage requiring intervention, severe maternal morbidity or maternal mortality, or spontaneous preterm delivery before 32 weeks of gestation.[78]

THYROID DISORDERS

The peak incidence of thyroid disease is in women of childbearing age. Hypoactivity and hyperactivity of the thyroid gland lead to obstetric complications and warrant specific therapy.

Hyperthyroidism

The most common cause of hyperthyroidism is Graves' disease, in which autoimmune thyroid-stimulating immunoglobulin results in increased production and release of thyroid hormone. Because the symptoms of hyperthyroidism resemble the physiologic changes expected during pregnancy in many respects, the diagnosis may not be immediately evident. Patients with Graves' disease have disease-specific findings, including a diffusely enlarged, soft, mildly tender thyroid gland, exophthalmos, and dermopathy. Other symptoms, such as dyspnea, heat intolerance, hyperemesis, tachycardia, palpitations, systolic flow murmurs, increased appetite, and fatigue, are common to both conditions. Therefore, clinically differentiating Graves' disease from non–Graves'-associated hyperthyroidism can be difficult. In cases of suspected hyperthyroidism, thyroid function studies and antibody assays are indicated and will confirm the presence of disease.

There are several obstetric concerns for the mother and fetus in the setting of untreated clinical hyperthyroidism (see Table 179.3). Thyroid storm is the most serious manifestation of the disease. It may be precipitated by stressors such as infection and delivery; it is manifested by fever, dysrhythmias, myocardial dysfunction, and circulatory collapse. The most helpful differentiating symptoms between thyrotoxicosis and thyroid storm is markedly altered mental status in the presence of thyroid storm. Untreated, mortality approaches 100%, but prompt recognition and aggressive therapy have lowered mortality to 20% to 30%.[83] In addition to the more general complications stemming from thyroid hormone excess, early (spontaneous abortion) and late (stillbirth) fetal loss are more common in hyperthyroid patients than in the general population.[84] Graves' disease places the fetus at risk for autoimmune-mediated thyroid dysfunction through placental transfer of maternal thyroid-stimulating immunoglobulins. Up to 20% of neonates of mothers with Graves' disease and positive thyroid-stimulating immunoglobulin values have transient hyperthyroidism lasting 3 to 12 weeks.[85] The condition gradually clears as maternal antibodies are metabolized. Manifestations are potentially severe and include irritability, tachycardia, goiter, cardiomegaly, congestive heart failure, premature craniosynostosis, low birth weight, and failure to thrive.[86]

The mainstay of treatment of hyperthyroidism (see Table 179.3) consists of antithyroid drugs. Propylthiouracil has been recommended as being preferred to methimazole because of an increased potential for adverse congenital drug effects from methimazole.[87] Most patients respond to pharmacologic manipulation, although thyroidectomy may be considered in severe cases in which patients cannot tolerate antithyroid medication or in the setting of medication failure. Use of iodine-131 radionuclide to ablate the maternal thyroid is contraindicated because it will also destroy the fetal thyroid gland.

Additional therapy with beta blockade to mitigate the hemodynamic effects of sympathetic stimulation may be required in certain cases pending adequate disease control with antithyroid medications. Iodide is considered class D in pregnancy because of fetal thyroid sensitivity to the medication; its use should be reserved for severe cases, with duration of therapy limited to days. As with other autoimmune conditions, transient improvement of Graves' disease during pregnancy is common, with rebound and clinical deterioration occurring in most patients after delivery.

Hypothyroidism

The most common cause of hypothyroidism worldwide is iodide deficiency. In iodine-replete areas, the most common cause is post autoimmune thyroiditis, such as Hashimoto's thyroiditis. Overt hypothyroidism is often associated with infertility, so most cases seen during pregnancy are less severe. Subclinical disease forms can also be seen or may occur in patients already undergoing levothyroxine therapy for known disease. Undiagnosed subclinical hypothyroidism may become clinically apparent as the metabolic demands of pregnancy unmask deficient thyroid hormone levels. When signs and symptoms do occur, they are generally the same as those in the nonpregnant state. Myxedema coma is extremely rare but should be considered along with other causes of coma in a pregnant patient. As with hyperthyroidism, there is an increased incidence of adverse maternal and fetal effects in women with clinical hypothyroidism (see Table 179.3).[88]

Most patients who are already undergoing treatment for hypothyroidism will require an increased dosage of levothyroxine during pregnancy, especially during the first trimester, in which average increases are from 20% to 30%.[89] Approximately 3% to 5% of women of childbearing age have subclinical hypothyroidism, as defined by an elevated thyroid-stimulating hormone (TSH) level and normal thyroxine (T_4) level. It has been noted that clinical and subclinical hypothyroidism result in adverse perinatal outcomes and adverse neurologic outcomes for affected infants. Compared with euthyroid status, subclinical hypothyroid pregnancy is associated with higher rates of gestational hypertension, premature rupture of membranes, intrauterine growth restriction (IUGR), and low-birth-weight infants.[90]

SYSTEMIC INFECTIONS

Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

Human immunodeficiency virus (HIV) infection is one of the leading health problems in pregnancy. In 2008, 25% of reported cases of HIV infection and acquired immunodeficiency syndrome (AIDS) in the United States were in women, with a significant percentage being in women of childbearing age.[91] Estimates of the seroprevalence of HIV infection in pregnant women vary on a regional basis. In the United States, the overall prevalence and number of perinatally infected infants are low but also vary according to the population, with increased rates seen in the southern states and in black and Hispanic populations.[91] Worldwide, vertical transmission of HIV remains a significant problem.

The mechanism of vertical transmission is multifactorial. Most cases are thought to occur during delivery through exposure to maternal blood and secretions; other infants are likely to be infected in utero or through breast-feeding. Various factors influence the rate of transmission. The most important is maternal viral load, although infection can occur even with a low maternal viral load.[92,93] Other contributing factors for transmission include inadequate prenatal care, vaginal infections, injection drug use,

premature delivery, low birth weight, and prolonged rupture of membranes.[92-94] Vertical transmission of HIV in the United States and other developed countries has declined significantly since its peak in the early 1990s because of the implementation of a number of interventions, including routine voluntary testing, highly active antiretroviral therapy (HAART), use of elective cesarean section, and avoidance of breast-feeding. However, vertical transmission remains a concern in women without adequate prenatal care and is a global concern. It is estimated that perinatal infection occurs in approximately 20% of deliveries if the mother is untreated, whereas the interventions noted have reduced this rate to less than 1%. Because of this beneficial effect, it is recommended that all pregnant women undergo screening for HIV. Rapid HIV screening is recommended for women in labor whose HIV status is unknown.[92,95]

Treatment of the pregnant patient with HIV infection includes appropriate HAART and standard therapy for opportunistic infections (see Table 179.3).[96,97] There are limited data on specific therapy for opportunistic infections during pregnancy, but the emergency clinician should take into account the fact that medication clearance may be affected by various pregnancy-related changes, including increased renal clearance, dilutional anemia, and fetal metabolism of medications.[98]

Optimal therapy to prevent vertical transmission includes three stages—antepartum administration of HAART, intrapartum intravenous zidovudine dosing, and treatment of the infant with 4 to 6 weeks of zidovudine.[92,99] The specific HAART regimen to follow depends on a number of variables. In patients who are already taking HAART with good disease control (viral load <1000 copies/mL) at the time of pregnancy diagnosis, the current medication regimen should be continued. Efavirenz (EFV) has teratogenic risks, with neural tube defect abnormalities prior to 6 weeks' gestation, so HIV-positive women planning to become pregnant should have this regimen changed. If a woman previously on EFV becomes pregnant, current recommendations are to continue the therapy, because most pregnancies are not diagnosed prior to 6 weeks, when the potential teratogenic effects of the medication have already been sustained.[92] Women who have never received any form of antiretroviral therapy are started on a standard multidrug HAART regimen that avoids the use of EFV in the first trimester. Delayed initiation of HAART until the second trimester may be considered in women if the only goal of therapy is to prevent mother to child transmission (maternal viral load < 1000 copies/mL).[92,99] In HIV-infected mothers without prenatal care, intrapartum HAART followed by postexposure zidovudine treatment of the infant reduces the likelihood of infection but is less effective than the recommended three-stage regimen.[92,100] Elective cesarean section is recommended in mothers with a viral load greater than 1000 copies/mL.[92] It is reasonable to present cesarean delivery as an option for patients with lower viral loads, although the benefit for these lower risk mothers is uncertain, and the risk of mother to child transmission by vaginal delivery is very low when mothers have received effective HAART.[92,101]

Whereas breast-feeding is associated with mother to child transmission of HIV infection and is not recommended in urban areas with access to formula preparations, it remains the preferred mode of feeding in resource-poor areas where formula use is not possible. WHO now encourages breast-feeding exclusively in women when adequate and safe formula feeding is not possible.[102]

The preferred means of diagnosis of perinatal HIV infection is by the use of assays to detect viral RNA or DNA. Two negative viral assays, with at least one after 4 months of age, means that the infant can be labeled seronegative. In addition, two negative tests after 6 months of age, with the absence of other clinical symptoms or suggestive laboratory findings, can be used to rule out infant disease. Infants with AIDS typically present with recurrent bacterial infections, *Pneumocystis* pneumonia, encephalopathy, extrapulmonary tuberculosis, and generalized wasting.

The effects of pregnancy in women with symptomatic HIV infection include an increased incidence of infant mortality, prematurity, stillbirth, and low birth weight, delivery by cesarean section, and gestational diabetes.[103-105] Seropositive mothers who undergo cesarean delivery generally have an uncomplicated postoperative course, although some studies have noted a slightly increased risk of postpartum endometritis and other maternal infections, with the highest rate of infection seen in women who have low CD4+ cell counts.[106] It is also important to consider the effect of HAART on pregnancy outcomes. Overall, however, most antiretroviral medications are considered safe in this regard. Several large studies have noted no increase in adverse outcomes in women taking HAART,[107] with the possible exception of preterm delivery, although this remains controversial.[108-110]

In the absence of retroviral therapy, HIV disease progression during pregnancy is moderate, and the risk of HIV negative outcomes increases. When HAART is used in pregnancy, there appears to be no increased risk of disease progression.[111]

Tuberculosis

It is estimated that tuberculosis (TB) complicates in excess of 200,000 pregnancies worldwide annually.[112] Most of these occur in Africa. The acquisition and presentation of TB are unchanged during pregnancy, but the effect of TB on pregnancy is unclear. Preconception, active genital TB disease increases the risk of an ectopic pregnancy.[113] Accurate assessment of the risk of maternal and neonatal morbidity has been difficult to ascertain,[114] but there seems to be consensus that complications are more likely in patients with inadequate or delayed diagnosis and treatment and in those with extrapulmonary (extranodal) tuberculosis. Delayed diagnosis is common in pregnancy because TB symptoms are atypical during gestation.[115,116] This is an even greater challenge in those patients co-infected with HIV who will likely fail WHO screening guidelines on surveillance for pulmonary TB (16% vs. >90% compared to nonpregnant women).[117] Neonatal tuberculosis acquired by exposure to undiagnosed and untreated active disease places infants at significant risk for acquiring tuberculosis during the first year of life, with significant mortality. In addition, congenital tuberculosis is possible after the fetus becomes infected through the placenta or via aspiration of infected amniotic fluid. The latter is rare if the mother has received appropriate therapy.

Definitive treatment is indicated in all pregnant patients with confirmed tuberculosis as well as in those high-risk women with suspected disease (see Table 179.3). Moderate to severe anemia, particularly in HIV-positive mothers, has a strong association with undiagnosed TB and should prompt screening.[118] Isoniazid, ethambutol, and rifampin in their usual doses have not been shown to be teratogenic to human fetuses and are acceptable during pregnancy and breast-feeding. Standardized, second-line treatment for multidrug resistant TB appears to be safe in pregnancy.[119]

Syphilis

The incidence of primary and secondary syphilis among US reproductive age women has steadily increased since the late 1990s, when there were hopes of eradicating the disease. Significant differences in ethnic distribution of the disease have been noted, with current rates of 4.5/100,000 in African Americans, 2.5/100,000 in Hispanics, and 1.0/100,000 in whites.[91] Unfortunately, the incidence of congenital syphilis has shown a similar increase from 2005 to 2008, with a current rate of 8.2/100,000 live births.[120]

Syphilis causes numerous gestational complications (see Table 179.3), but its most significant sequela is congenital syphilis. This syndrome is characterized by hepatosplenomegaly, osteochondritis, jaundice, rash, lymphadenopathy, rhinitis, Hutchinson's teeth, and anemia. Infant mortality for cases within the last decade was 6.5%.[120] Fetal ultrasonography before the 20th week of gestation is indicated to assess for abnormalities consistent with congenital syphilis.[71,72,95] Sonographic signs of fetal syphilis confer a higher risk of congenital syphilis at delivery, and few of these completely regress after sufficient treatment.[72]

Treatment is identical to that given to nonpregnant patients, with the use of benzathine penicillin G appropriate for the disease stage[71] (see Table 179.3). Penicillin-allergic patients are sometimes treated with macrolides. However, it is preferable that these patients undergo skin testing and desensitization if the skin test result is positive because alternative therapies are not reliably effective in preventing congenital syphilis.[95] Treatment failures are rare with appropriately administered penicillin, but do occur. Failures leading to congenital syphilis are more likely in mothers with secondary syphilis, high Venereal Disease Research Laboratory or rapid plasma reagin test levels, and an interval from treatment to delivery of less than 30 days.[95]

Viral Hepatitis

Hepatitis B

There are 43,000 new cases of Hepatitis B reported annually in the United States, but this is likely an underestimation of disease burden, given the absence of symptoms in early infection.[121] From 800,000 to 1.4 million people in the United States have chronic hepatitis B. The prevalence of hepatitis B virus (HBV) infection among pregnant women varies by the population studied, with the highest rates seen in Asians and women of African descent.[122] Perinatal transmission is approximately 10% to 20% in women seropositive for HBV surface antigen (HBsAg) alone but approaches 90% in mothers who are seropositive for HBsAg and HBV envelope antigen (HBeAg); it is also more likely if the mother has acute infection during the third trimester. Of infants who have HBV infection, up to 90% become chronic carriers as adults and are at risk for complications such as cirrhosis and hepatocellular carcinoma.

Studies have suggested that lamivudine given in late pregnancy to women with high viral loads of HBV DNA reduces viral transmission when given in conjunction with HBV vaccine and immune globulin.[123] Infants of HBsAg-positive mothers should receive hepatitis B immune globulin and the first dose of vaccine within 12 hours of birth. Two additional doses of vaccine are administered at a later date.[73]

Hepatitis C

The worldwide prevalence of hepatitis C virus (HCV) infection in pregnant women is estimated to be between 1% and 8%.[124] As with HBV, the prevalence of hepatitis C virus (HCV) infection among pregnant women varies by geographic location and ethnic subculture within a population, ranging from less than 1% to approximately 4%, with white mothers having higher infection rates than black or Hispanic mothers. Vertical transmission is rare in mothers with anti-HCV antibodies and no circulating HCV RNA. However, perinatal transmission is significantly increased by the presence of HCV viremia, occurring in approximately 4% to 6% of cases. The transmission rate is even higher in the setting of co-infection with HIV; the rates of HCV co-infectivity with HIV are about 10-fold higher than that seen in non–HIV-infected mothers. Perinatal transmission is now the leading cause of HCV transmission to children in developed countries. Cesarean delivery has not been shown to prevent HCV transmission.[95,125] There is no available vaccine or immune globulin to prevent hepatitis C, and routine prenatal screening is not indicated.[95,125]

INFLAMMATORY DISORDERS

Rheumatic diseases or collagen vascular diseases are characterized by sterile inflammation in multiple anatomic sites. The most common rheumatic diseases encountered in pregnancy are systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Gravid patients with collagen vascular disease may have preexisting cardiovascular or renal compromise and may not tolerate the increased intravascular volume and other physiologic changes that occur during pregnancy.

Systemic Lupus Erythematosus

SLE primarily affects women of reproductive age, but fertility is usually unaffected. The disease course during pregnancy varies, but studies have indicated that acute flares occur in less than one-third of patients in clinical remission at the time of conception.[126-128] Disease activity tends to involve the skin and musculoskeletal system, although renal involvement is not uncommon, especially in patients with active lupus nephritis.[129,130] The gestational effects of SLE also depend on the underlying severity of disease. Patients with active disease at pregnancy onset with symptoms of hypertension, thrombocytopenia and, especially those with preexisting lupus nephritis, have a higher incidence of disease flares and pregnancy complications.[126,128,130,131] Many patients have acceptable outcomes, but lupus pregnancies are associated with an increased maternal mortality and increased rate of other complications, including preterm delivery, thrombocytopenia, anemia, intrauterine growth retardation, fetal loss, and need for cesarean section.[126,132]

The risk of preeclampsia is increased up to 14% in lupus-related pregnancies; initiation of low-dose aspirin therapy prior to 16 weeks' gestation decreases the risk of preeclampsia.[133] The development of preeclampsia in women with a history of SLE seems to have a predictive association with subclinical coronary vascular disease.[134] This should prompt consideration of less exertional delivery methods as well as drive postpartum medical decision making to evaluate for coronary artery disease.

Other comorbid conditions that adversely affect pregnancy, such as diabetes and thrombophilia, are also seen more commonly in SLE patients. The risk of preeclampsia is especially increased in those with active lupus nephritis.[128,130] As with other renal disease, increasing proteinuria warrants a careful evaluation to distinguish between lupus glomerulonephritis and preeclampsia. The presence of abnormal urine sediment, increasing titers of anti-DNA antibody, and decreasing levels of C3 and C4 suggest lupus nephritis.

Neurologic disease in SLE may be manifested as psychosis, seizures, chorea, or peripheral neuropathy. The incidence of these complications is low during pregnancy, although the occurrence of seizures in late pregnancy in patients with coexistent hypertension and renal insufficiency may pose a diagnostic dilemma between the neurologic effects of SLE and signs of eclampsia. Elevated levels of lupus anticoagulant and antiphospholipid antibodies have emerged as markers of disease activity and are good predictors for adverse pregnancy outcomes.[135]

Rheumatoid Arthritis

RA is characterized by chronic, destructive, symmetric joint inflammation. Less common manifestations include the development of subcutaneous nodules, neuropathy, pleuropericarditis, and vasculitis. Systemic symptoms, including weight loss,

lymphadenopathy, and fatigue, are common. Because the median age at onset is later with RA, this disorder is seen less frequently than SLE in the pregnant population. Immune tolerance mechanisms are upregulated in pregnancy to decrease fetal rejection. In rheumatic diseases, this typically results in disease improvement, which has been estimated to occur in approximately two-thirds of patients with RA.

Patients with RA tend to have good pregnancy outcomes in the setting of well-controlled disease. Women with active disease are more likely to have small-for-gestational-age infants, possibly as a result of underlying vasculopathy and associated effects on the placenta.

Treatment

Corticosteroids are the mainstay of therapy for most rheumatologic complications or exacerbations. Aspirin has been advocated for all lupus-related pregnancies of more than 16 weeks' gestational age, and other NSAID regimens remain useful treatments for inflammatory flares. A full discussion on fetal teratogenicity and fetal complications of these agents can be found in Chapter 180.

Second-line therapy for rheumatic diseases can include cytotoxic agents such as cyclophosphamide and methotrexate. These are both potent teratogens and abortifacients and should be avoided, especially in the first trimester. Azathioprine is a cytotoxic agent that appears to be much better tolerated in pregnancy.[135,136]

PSYCHIATRIC DISORDERS

Eating Disorders

The peak incidence of eating disorders matches that of those in the prime childbearing age range, so the likelihood of anorexia nervosa (AN) or bulimia nervosa (BN) complicating a pregnancy is high. The overall prevalence of AN is 0.5% to 1% of young adult women, with a mean age of onset of 17 years, and an overall prevalence of BN of 1% to 3% in the same population.[137] Of all eating disorders, 90% begin before the age 25 years, and there has historically been an increased incidence of all eating disorder diagnoses in the past decade. The high incidence of amenorrhea in AN makes pregnancy less likely than in BN. Medical complications of AN include bradycardia, hypotension, orthostatic changes, hypothermia, mitral valve prolapse, and symptoms associated with electrolyte imbalance. Anemia and transaminitis are also seen.

Pregnancy can frequently precipitate a subclinical eating disorder or exacerbate a condition in remission. The loss of control of body image and weight gain are frequent inciting features for recurrence. Adverse pregnancy outcomes include increased rates of miscarriage, low birth weight, preterm birth, congenital malformations, and increased likelihood of cesarean section births.[138] Inappropriate dieting, with subsequent folate deficiency, increases the rate of congenital neural tube defects. In the postpartum period, depression risk is increased threefold in mothers with a history of eating disorders.

Treatment of any eating disorder during pregnancy is aimed at the restoration of normal physiologic parameters, electrolyte replacement, and correction of ketosis. There are no recommended pharmacologic interventions for AN by the US Food and Drug Administration, but antidepressant therapy may be beneficial in those with exacerbations of BN.[139]

Substance Abuse

The prevalence of substance abuse in pregnancy has been increasing, with major societal and personal costs. Substance abuse is frequently not identified during pregnancy unless self-reported, or an unplanned pregnancy is discovered during the evaluation of the mother for a substance-related disorder. This is particularly common in the ED, where women of childbearing age are seen frequently for associated complications and pregnancy is coincidentally identified during the visit.

The overall rate of substance use and abuse in pregnancy is approximately 15%. The rate has been steadily increasing in the last 3 decades, with roughly 225,000 infants annually exposed to illicit drugs in utero.[140] Drug use and dependence afflict women, regardless of socioeconomic status, ethnicity, or age. Although illicit drug use is more common in African Americans, alcohol, cannabis, and prescriptive drug use are most commonly seen in white women.

The impact of substance abuse on pregnancy is determined by the following: (1) specific exposure (mono- vs. polysubstance abuse); (2) gestational timing; (3) duration of exposure; (4) dosing of exposure; and (5) other maternal comorbid conditions (eg, smoking, general nutritional status). There is a strong association of substance abuse with psychiatric conditions, particularly depression and psychosis.

Within this context, the terms *abuse* and *dependence* will be used synonymously, although they are different clinical entities. Both conditions have the same impact on maternal and neonatal health and pregnancy-related complications.

Alcohol

Of women of childbearing age, 51% self-identify as alcohol users and 15% are binge drinkers.[141] Nearly 2 million women annually are at risk for alcohol-exposed pregnancies, defined as women who are not using birth control, currently drinking, and are sexually active with a man.[142] Once pregnancy has been identified, the rate of active alcohol consumption in gravid women drops to 7%, and binge drinking to lower than 2%.[143]

There is no clear safe threshold for alcohol intake during pregnancy, with intake as little as one drink/day being associated with increased rates of IUGR and low birth weight. Heavier consumption of alcohol at more than three drinks/day increases the rate of miscarriage, and more than five drinks/day significantly increases the risk of intrauterine fetal demise (IUFD) two to three times that of nondrinking mothers. Alcohol consumption in pregnancy is the most preventable cause of mental retardation, with alcohol-exposed children having a 1.7-fold greater relative risk of mental retardation and a 2.5 times greater risk of delinquent behaviors.

Congenital abnormalities associated with in utero alcohol exposure can be characterized within the fetal alcohol spectrum disorders. Fetal alcohol syndrome, the most severe of these, has a prevalence of up to 1/1000 births.[143] It is characterized by at least one of a series of morphologic abnormalities in association with a history of heavy alcohol use (>three drinks/day), including midfacial hypoplasia, flat philtrum, low nasal bridge, epicanthal folds, shortened palpebral fissure, low-set ears, and microcephaly. It can also have ocular, cardiac, and skeletal manifestations.

Screening is imperative to identify at-risk pregnancies, and the most successful screening tools assume the presence of alcohol intake. This approach yields more honest reporting from the patient.[144]

Treatment of an alcohol-dependent mother is difficult. As with nonpregnant patients, withdrawal symptoms are likely to manifest 6 to 24 hours after last alcohol consumption. Any signs of withdrawal should prompt admission and continued management in an inpatient setting. There is a paucity of data on the risk of delirium tremens and major withdrawal in pregnant versus the nonpregnant population. There are also little data on the safety profiles of medications used to ameliorate withdrawal

symptoms.[145] The use of naltrexone, acamprosate, or disulfiram or the long-term use of benzodiazepines has not been studied in pregnancy.

Smoking

The long-term deleterious effects of smoking on fetal growth and development have been well documented, up to and including the risk of sudden infant death syndrome (SIDS).[146] Chronic placental insufficiency and vasoconstriction lead to an increased risk of miscarriage, IUFD, preterm birth, IUGR, and clubfoot.[147] Conversely, smoking decreases the risk of preeclampsia.[148]

Treatment for tobacco addiction in pregnancy is largely behavioral and cognitive. Nicotine patches have not been associated with adverse maternal or newborn consequences when used in the second and third trimesters.

Cannabis

Cannabis is the most commonly used illicit drug in pregnancy.[149] Although marijuana use in pregnancy is not associated with any major congenital malformations or increased risk of IUFD, infants born to cannabis-using mothers show increased tremulousness, exaggerated startle responses, and high-pitched cries. These are some of the same features associated with neonatal abstinence syndrome (NAS) discussed later in more detail (see "Opioids"). Cannabis is excreted in breast milk and has been associated with neurologic impairment during continued exposure.[149]

Cocaine and Methamphetamines

Maternal cocaine and methamphetamine use is independently linked to IUGR from impaired placental circulation and preterm birth (PTB) less than 36 weeks' gestation, preeclampsia, IUFD, and increased incidence of cesarean section, gestational hypertension, and GDM.[149,150] Cocaine use also increases the risk of placental abruption and infarction. Infants of methamphetamine- addicted mothers have lower Apgar scores and increased rates of neonatal mortality and jaundice.[150] The potential for adverse outcomes is increased in the presence of polysubstance abuse or other confounding maternal risks, such as poor nutrition. Neonatal congenital abnormalities do not seem to be significantly increased with cocaine use, although there is a slight increased risk of cleft palate with cocaine exposure.

Treatment of a gravid patient who is acutely intoxicated with cocaine or methamphetamine should involve the judicious use of benzodiazepines and antipsychotics, weighing the risk-benefit ratio for treatment against the medical and psychiatric instability of the patient. Methamphetamine is excreted in breast milk, so infant exposure continues after pregnancy.[150]

Opioids

Roughly 1% of pregnant patients report opioid use during pregnancy, but drug testing proves this number to be higher, around 4%. In general, usage rates have been significantly increasing,[151,152] which has created a downstream effect of large numbers of addicted infants requiring neonatal intensive care. There is a significant risk of unintended pregnancy among opioid-addicted women, close to 90%, compared to the unintended pregnancy rate in the general population of 40%.[153] The ED is a likely site of entrance of the opioid-addicted gravid patient to the health care system.

There are no well-identified syndromes, congenital abnormalities, or teratogenic effects in infants of opioid-dependent mothers, but maternal risks of postpartum hemorrhage, PTB, and increased rates of cesarean section have been documented.[154] Neonatal risks include IUGR, specifically symmetric smallness and small head circumference,[155] and an increased risk of SIDS.[156] The major complication in infants of opioid-addicted mothers is NAS, a constellation of physiologic and neurobehavioral changes noted in newborns of addicted mothers secondary to a sudden discontinuation of fetal exposure to abused substances. There has been a 10-fold increase in NAS within the last decade.[157] These infants have a 97% admission rate to neonatal intensive care units.

The syndrome is characterized by the following: (1) CNS disturbances, including excessive or continuous high- pitched crying, shortened postprandial sleep pattern, hyperactive newborn reflexes, tremulousness, and increased muscle tone, myoclonic jerks, or frank convulsions; (2) metabolic and respiratory abnormalities (eg, sweating, hyperthermia, yawning, mottling, sneezing, nasal flaring, tachypnea); and (3) gastrointestinal disturbances (eg, increased sucking, poor feeding, regurgitation or projectile vomiting, loose or watery stools). The Finnegan scale, developed in the 1970s, is still the mainstay of neonatal assessment for NAS. Treatment of NAS is supportive.

KEY CONCEPTS

- The physiologic demands of pregnancy may cause previously occult medical conditions to become apparent and known problems to deteriorate rapidly.
- The physiologic adjustments of pregnancy alter the normal ranges for certain laboratory values. The adjusted values need to be considered in the interpretation of results.
- The possibility of pregnancy should be considered in the differential diagnosis of certain conditions, including new-onset seizures or status epilepticus (eclampsia), glucose intolerance (GDM), persistent vomiting (hyperemesis gravidarum), and thyroid disorders.
- The immunosuppressive effects of pregnancy may cause temporary improvement in inflammatory and autoimmune conditions. This beneficial effect is lost in the postpartum period, resulting in exacerbations of asthma, thyroid disorders, and myasthenia gravis.
- Medication requirements can change drastically during pregnancy and the postpartum period.
- Certain medical conditions in the mother result in neonatal complications that require special resuscitative measures. This is particularly true of many chemical dependency states, and anticipatory management of these patients is essential.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

REFERENCES

1. Rejno G, Lundholm C, Gong T, et al: Asthma during pregnancy in a population-based study—pregnancy complications and adverse perinatal outcomes. PLoS ONE 9:e104755, 2014.
2. Namazy JA, Murphy VE, Powell H, et al: Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. Eur Respir J 41:1082–1090, 2013.
3. Rocklin RE: Asthma, asthma medications and their effects on maternal/fetal outcomes during pregnancy. Reprod Toxicol 32:189–197, 2011.
4. Namazy JA, Chambers C, Schatz M: Safety of therapeutic options for treating asthma in pregnancy. Expert Opin Drug Saf 13:1613–1621, 2014.
5. Breton MC, Beauchesne MF, Lemière C, et al: Risk of perinatal mortality associated with inhaled corticosteroid use for the treatment of asthma during pregnancy. J Allergy Clin Immunol 126:772–777.e2, 2010.
6. Cossette B, Beauchesne MF, Forget A, et al: Systemic corticosteroids for the treatment of asthma exacerbations during and outside of pregnancy in an acute-care setting. Respir Med 108:1260–1267, 2014.
7. McCallister JW, Benninger CG, Frey HA, et al: Pregnancy-related treatment disparities of acute asthma exacerbations in the emergency department. Respir Med 105:1434–1440, 2011.
8. Committee on Obstetric Practice: Committee opinion no. 514: Emergent therapy for acute-onset, severe hypertension with preeclampsia or eclampsia. Obstet Gynecol 118:1465–1468, 2011.
9. Too GT, Hill JB: Hypertensive crisis during pregnancy and postpartum period. Semin Perinatol 37:280–287, 2013.
10. Simpson LL: Maternal cardiac disease: Update for the clinician. Obstet Gynecol 119(Pt 1):345–359, 2012.
11. Kuklina E, Callaghan W: Chronic heart disease and severe obstetric morbidity among hospitalisations for pregnancy in the USA: 1995-2006. BJOG 118:345–352, 2011.
12. European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, et al: ESC guidelines on the management of cardiovascular diseases during pregnancy: The task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). Eur Heart J 32:3147–3197, 2011.
13. Bramham K, Parnell B, Nelson-Piercy C, et al: Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ 348:g2301, 2014.
14. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy: Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol 122:1122–1131, 2013.
15. Seely EW, Ecker J: Chronic hypertension in pregnancy. Circulation 129:1254–1261, 2014.
16. Raheem IA, Saaid R, Omar SZ, et al: Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. BJOG 119:78–85, 2012.
17. Ersboll AS, Hedegaard M, Sondergaard L, et al: Treatment with oral beta-blockers during pregnancy complicated by maternal heart disease increases the risk of fetal growth restriction. BJOG 121:618–626, 2014.
18. Simpson LL: Maternal cardiac disease: Update for the clinician. Obstet Gynecol 119(Pt 1):345–359, 2012.
19. Kealey A: Coronary artery disease and myocardial infarction in pregnancy: a review of epidemiology, diagnosis, and medical and surgical management. Can J Cardiol 26:185–189, 2010.
20. Fryearson J, Adamson DL: Heart disease in pregnancy: ischaemic heart disease. Best Pract Res Clin Obstet Gynaecol 28:551–562, 2014.
21. Turitz AL, Friedman AM: Ischemic heart disease in pregnancy. Semin Perinatol 38:304–308, 2014.
22. Cantwell R, Clutton-Brock T, Cooper G, et al: Mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 118(Suppl 1):1–203, 2011.
23. Nanna M, Stergiopoulos K: Pregnancy complicated by valvular heart disease: an update. J Am Heart Assoc 3:e000712, 2014.
24. Roos-Hesselink JW, Ruys TP, Stein JI, et al: Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. Eur Heart J 34:657–665, 2013.
25. Nishimura RA, Otto CM, Bonow RO, et al: 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. Circulation 129:e521–e643, 2014.
26. Howlett JG, McKelvie RS, Costigan J, et al: The 2010 Canadian Cardiovascular Society guidelines for the diagnosis and management of heart failure update: heart failure in ethnic minority populations, heart failure and pregnancy, disease management, and quality improvement/assurance programs. Can J Cardiol 26:185–202, 2010.
27. Windram JD, Colman JM, Wald RM, et al: Valvular heart disease in pregnancy. Best Pract Res Clin Obstet Gynaecol 28:507–518, 2014.
28. Pieper PG, Lameijer H, Hoendermis ES: Pregnancy and pulmonary hypertension. Best Pract Res Clin Obstet Gynaecol 28:579–591, 2014.
29. European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, et al: ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 32:3147–3197, 2011.
30. Sukrat B, Wilasrusmee C, Siribumrungwong B, et al: Hemoglobin concentration and pregnancy outcomes: a systematic review and meta-analysis. Biomed Res Int 2013:769057, 2013.
31. Goonewardene M, Shehata M, Hamad A: Anaemia in pregnancy. Best Pract Res Clin Obstet Gynaecol 26:3–24, 2012.
32. World Health Organization: Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. <www.who.int/vmnis/indicators/haemoglobin/en>.
33. Borthen I, Eide MG, Daltveit AK, et al: Delivery outcome of women with epilepsy: a population-based cohort study. BJOG 117:1537–1543, 2010.
34. Horowitz KM, Ingardia CJ, Borgida AF: Anemia in pregnancy. Clin Lab Med 33:281–291, 2013.
35. Rohilla M, Raveendran A, Dhaliwal LK, et al: Severe anaemia in pregnancy: a tertiary hospital experience from northern India. J Obstet Gynaecol 30:694–696, 2010.
36. Haider BA, Olofin I, Wang M, et al, Nutrition Impact Model Study Group (Anaemia): Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. BMJ 346:f3443, 2013.
37. Imdad A, Bhutta ZA: Routine iron/folate supplementation during pregnancy: effect on maternal anaemia and birth outcomes. Paediatr Perinat Epidemiol 26(Suppl 1):168–177, 2012.
38. Pena-Rosas JP, De-Regil LM, Dowswell T, et al: Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev (12):CD004736, 2012.
39. Reveiz L, Gyte GM, Cuervo LG, et al: Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database Syst Rev (5):CD003094, 2011.
40. Fekete K, Berti C, Trovato M, et al: Effect of folate intake on health outcomes in pregnancy: a systematic review and meta-analysis on birth weight, placental weight and length of gestation. Nutr J 11:75, 2012.
41. Fekete K, Berti C, Cetin I, et al: Perinatal folate supply: relevance in health outcome parameters. Matern Child Nutr 6:23–38, 2010.
42. Lamers Y: Folate recommendations for pregnancy, lactation, and infancy. Ann Nutr Metab 59:32–37, 2011.
43. Centers for Disease Control and Prevention: Folic acid: recommendations. <www.cdc.gov/ncbddd/folicacid/recommendations.html>.
44. Al Kahtani MA, AlQahtani M, Alshebaily MM, et al: Morbidity and pregnancy outcomes associated with sickle cell anemia among saudi women. Int J Gynaecol Obstet 119:224–226, 2012.
45. Ngo C, Kayem G, Habibi A, et al: Pregnancy in sickle cell disease: maternal and fetal outcomes in a population receiving prophylactic partial exchange transfusions. Eur J Obstet Gynecol Reprod Biol 152:138–142, 2010.
46. Howard J, Oteng-Ntim E: The obstetric management of sickle cell disease. Best Pract Res Clin Obstet Gynaecol 26:25–36, 2012.
47. Parrish MR, Morrison JC: Sickle cell crisis and pregnancy. Semin Perinatol 37: 274–279, 2013.
48. Okusanya BO, Oladapo OT: Prophylactic versus selective blood transfusion for sickle cell disease in pregnancy. Cochrane Database Syst Rev (12):CD010378, 2013.
49. Hart LA, Sibai BM: Seizures in pregnancy: epilepsy, eclampsia, and stroke. Semin Perinatol 37:207–224, 2013.
50. Kamyar M, Varner M: Epilepsy in pregnancy. Clin Obstet Gynecol 56:330–341, 2013.
51. Vajda FJ, O'Brien TJ, Lander CM, et al: The teratogenicity of the newer antiepileptic drugs—an update. Acta Neurol Scand 130:234–238, 2014.
52. Mawhinney E, Craig J, Morrow J, et al: Levetiracetam in pregnancy: results from the UK and Ireland epilepsy and pregnancy registers. Neurology 80:400–405, 2013.
53. Tomson T, Battino D, Bonizzoni E, et al, EURAP study group: Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 10:609–617, 2011.
54. Hernandez-Diaz S, Smith CR, Shen A, et al, North American AED Pregnancy Registry: Comparative safety of antiepileptic drugs during pregnancy. Neurology 78:1692–1699, 2012.
55. Vajda FJ, O'Brien T, Lander C, et al: The efficacy of the newer antiepileptic drugs in controlling seizures in pregnancy. Epilepsia 55:1229–1234, 2014.
56. Hughes SE, Spelman T, Gray OM, et al: Predictors and dynamics of postpartum relapses in women with multiple sclerosis. Mult Scler 20:739–746, 2014.
57. Houtchens M: Multiple sclerosis and pregnancy. Clin Obstet Gynecol 56:342–349, 2013.
58. Amato MP, Portaccio E, Ghezzi A, et al: Pregnancy and fetal outcomes after interferon-beta exposure in multiple sclerosis. Neurology 75:1794–1802, 2010.
59. Lu E, Wang BW, Guimond C, et al: Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. Neurology 79:1130–1135, 2012.
60. Camune BD: Challenges in the management of the pregnant woman with spinal cord injury. J Perinat Neonatal Nurs 27:225–231, 2013.
61. Morton C, Le JT, Shahbandar L, et al: Pregnancy outcomes of women with physical disabilities: a matched cohort study. PM R 5:90–98, 2013.
62. Almeida C, Coutinho E, Moreira D, et al: Myasthenia gravis and pregnancy: anaesthetic management—a series of cases. Eur J Anaesthesiol 27:985–990, 2010.
63. Varner M: Myasthenia gravis and pregnancy. Clin Obstet Gynecol 56:372–381, 2013.
64. Norwood F, Dhanjal M, Hill M, et al: Myasthenia in pregnancy: best practice guidelines from a U.K. multispecialty working group. J Neurol Neurosurg Psychiatry 85:538–543, 2014.
65. Luders C, Castro MC, Titan SM, et al: Obstetric outcome in pregnant women on long-term dialysis: a case series. Am J Kidney Dis 56:77–85, 2010.
66. Piccoli GB, Attini R, Vasario E, et al: Pregnancy and chronic kidney disease: a challenge in all CKD stages. Clin J Am Soc Nephrol 5:844–855, 2010.
67. McCance DR: Pregnancy and diabetes. Best Pract Res Clin Endocrinol Metab 25:945–958, 2011.

68. Gunatilake RP, Perlow JH: Obesity and pregnancy: clinical management of the obese gravida. Am J Obstet Gynecol 204:106–119, 2011.
69. Jensen DM, Damm P, Ovesen P, et al: Microalbuminuria, preeclampsia, and preterm delivery in pregnant women with type 1 diabetes: results from a nationwide Danish study. Diabetes Care 33:90–94, 2010.
70. Klemetti MM, Teramo K, Nuutila M, et al: Blood pressure levels but not hypertensive complications have increased in type 1 diabetes pregnancies during 1989-2010. Diabet Med 30:1087–1093, 2013.
71. Clement ME, Okeke NL, Hicks CB: Treatment of syphilis: a systematic review. JAMA 312:1905–1917, 2014.
72. Rac MW, Bryant SN, McIntire DD, et al: Progression of ultrasound findings of fetal syphilis after maternal treatment. Am J Obstet Gynecol 211:426.e1–426.e6, 2014.
73. National Center for Immunization and Respiratory Diseases: General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 60:1–64, 2011.
74. Tennant PW, Bilous RW, Prathapan S, et al: Risk and recurrence of serious adverse outcomes in the first and second pregnancies of women with preexisting diabetes. Diabetes Care 38:610–619, 2015.
75. Negrato CA, Mattar R, Gomes MB: Adverse pregnancy outcomes in women with diabetes. Diabetol Metab Syndr 4:41, 2012.
76. Lai FY, Johnson JA, Dover D, et al: Outcomes of singleton and twin pregnancies complicated by pre-existing diabetes and gestational diabetes: a population-based study in Alberta, Canada, 2005-11. J Diabetes 8:45–55, 2016.
77. Ogden CL, Carroll MD, Flegal KM: Prevalence of obesity in the united states. JAMA 312:189–190, 2014.
78. Schummers L, Hutcheon JA, Bodnar LM, et al: Risk of adverse pregnancy outcomes by prepregnancy body mass index: a population-based study to inform prepregnancy weight loss counseling. Obstet Gynecol 125:133–143, 2015.
79. Bogaerts A, Devlieger R, Van den Bergh BR, et al: Obesity and pregnancy, an epidemiological and intervention study from a psychosocial perspective. Facts Views Vis Obgyn 6:81–95, 2014.
80. Gilead R, Yaniv Salem S, Sergienko R, et al: Maternal "isolated" obesity and obstetric complications. J Matern Fetal Neonatal Med 25:2579–2582, 2012.
81. Ayres-de-Campos D: Obesity and the challenges of cesarean delivery: prevention and management of wound complications. Best Pract Res Clin Obstet Gynaecol 29:406–414, 2015.
82. Meehan S, Beck CR, Mair-Jenkins J, et al: Maternal obesity and infant mortality: a meta-analysis. Pediatrics 133:863–871, 2014.
83. Devereaux D, Tewelde SZ: Hyperthyroidism and thyrotoxicosis. Emerg Med Clin North Am 32:277–292, 2014.
84. Andersen SL, Olsen J, Wu CS, et al: Spontaneous abortion, stillbirth and hyperthyroidism: A Danish population-based study. Eur Thyroid J 3:164–172, 2014.
85. Gietka-Czernel M, Debska M, Kretowicz P, et al: Hyperthyroidism during pregnancy—the role of measuring maternal TSH receptor antibodies and foetal ultrasound monitoring. Endokrynol Pol 65:259–268, 2014.
86. Cooper DS, Laurberg P: Hyperthyroidism in pregnancy. Lancet Diabetes Endocrinol 1:238–249, 2013.
87. Clementi M, Di Gianantonio E, Cassina M, et al, SAFE-Med Study Group: Treatment of hyperthyroidism in pregnancy and birth defects. J Clin Endocrinol Metab 95:E337–E341, 2010.
88. Sahu MT, Das V, Mittal S, et al: Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome. Arch Gynecol Obstet 281:215–220, 2010.
89. Hubaveshka J, Michaelsson LF, Nygaard B: The dose of levothyroxine in pregnant women with hypothyroidism should be increased by 20-30% in the first trimester. Dan Med J 61:A4959, 2014.
90. Chen LM, Du WJ, Dai J, et al: Effects of subclinical hypothyroidism on maternal and perinatal outcomes during pregnancy: a single-center cohort study of a Chinese population. PLoS ONE 9:e109364, 2014.
91. Centers for Disease Control and Prevention: 2013 sexually transmitted disease surveillance. <www.cdc.gov/std/stats13>.
92. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission: Recommendations for use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. <http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf>.
93. Tubiana R, Le Chenadec J, Rouzioux C, et al: Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). Clin Infect Dis 50:585–596, 2010.
94. Del Bianco G, Bell CS, Benjamins LJ, et al: Persistently high perinatal transmission of HIV: assessment of risk factors. Pediatr Infect Dis J 33:e151–e157, 2014.
95. Workowski KA, Berman S, Centers for Disease Control and Prevention (CDC): Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 59(RR–12):1–110, 2010.
96. Cressman AM, Natekar A, Kim E, et al: Cocaine abuse during pregnancy. J Obstet Gynaecol Can 36:628–631, 2014.
97. Pessel C, Bonanno C: Valve disease in pregnancy. Semin Perinatol 38:273–284, 2014.
98. Taylor AW, Mosimaneotsile B, Mathebula U, et al: Pregnancy outcomes in HIV-infected women receiving long-term isoniazid prophylaxis for tuberculosis and antiretroviral therapy. Infect Dis Obstet Gynecol 2013:195637, 2013.
99. World Health Organization: Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. <http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf>.
100. Senise J, Bonafe S, Castelo A: The management of HIV-infected pregnant women. Curr Opin Obstet Gynecol 24:395–401, 2012.
101. European Collaborative Study, Boer K, England K, et al: Mode of delivery in HIV-infected pregnant women and prevention of mother-to-child transmission: changing practices in western Europe. HIV Med 11:368–378, 2010.
102. World Health Organization: Guidelines on HIV and infant feeding, 2010. <http://whqlibdoc.who.int/publications/2010/9789241599535_eng.pdf>.
103. Kurewa EN, Gumbo FZ, Munjoma MW, et al: Effect of maternal HIV status on infant mortality: evidence from a 9-month follow-up of mothers and their infants in Zimbabwe. J Perinatol 30:88–92, 2010.
104. Joh O, Biodun O, Michael E: Pregnancy outcome among HIV-positive women receiving antenatal HAART versus untreated maternal HIV infection. J Coll Physicians Surg Pak 21:356–359, 2011.
105. Aebi-Popp K, Lapaire O, Glass TR, et al: Pregnancy and delivery outcomes of HIV-infected women in Switzerland 2003-2008. J Perinat Med 38:353–358, 2010.
106. Maiques V, Garcia-Tejedor A, Diago V, et al: Perioperative cesarean delivery morbidity among HIV-infected women under highly active antiretroviral treatment: a case-control study. Eur J Obstet Gynecol Reprod Biol 153:27–31, 2010.
107. Tookey P, Thorne C, Martinez-Tristani M, et al: Outcomes related to 4864 pregnancies with exposure to lopinavir/ritonavir (LPV/r). J Int AIDS Soc 17(Suppl 3):19613, 2014.
108. Sturt AS, Dokubo EK, Sint TT: Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. Cochrane Database Syst Rev (3): CD008440, 2010.
109. Townsend C, Schulte J, Thorne C, et al, Pediatric Spectrum of HIV Disease Consortium, European Collaborative Study and National Study of HIV in Pregnancy and Childhood: Antiretroviral therapy and preterm delivery—a pooled analysis of data from the United States and Europe. BJOG 117:1399–1410, 2010.
110. Patel K, Shapiro DE, Brogly SB, et al, P1025 team of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group: Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. J Infect Dis 201:1035–1044, 2010.
111. Calvert C, Ronsmans C: Pregnancy and HIV disease progression: a systematic review and meta-analysis. Trop Med Int Health 20:122–145, 2015.
112. Sugarman J, Colvin C, Moran AC, et al: Tuberculosis in pregnancy: an estimate of the global burden of disease. Lancet Glob Health 2:e710–e716, 2014.
113. Sharma JB, Naha M, Kumar S, et al: Genital tuberculosis: an important cause of ectopic pregnancy in India. Indian J Tuberc 61:312–317, 2014.
114. Lin HC, Lin HC, Chen SF: Increased risk of low birthweight and small for gestational age infants among women with tuberculosis. BJOG 117:585–590, 2010.
115. Loto OM, Awowole I: Tuberculosis in pregnancy: a review. J Pregnancy 2012:379271, 2012.
116. Nguyen HT, Pandolfini C, Chiodini P, et al: Tuberculosis care for pregnant women: a systematic review. BMC Infect Dis 14:617, 2014.
117. Hoffmann CJ, Variava E, Rakgokong M, et al: High prevalence of pulmonary tuberculosis but low sensitivity of symptom screening among HIV-infected pregnant women in South Africa. PLoS ONE 8:e62211, 2013.
118. Kerkhoff AD, Wood R, Vogt M, et al: Predictive value of anemia for tuberculosis in HIV-infected patients in sub-Saharan Africa: an indication for routine microbiological investigation using new rapid assays. J Acquir Immune Defic Syndr 66:33–40, 2014.
119. Tabarsi P, Moradi A, Baghaei P, et al: Standardised second-line treatment of multidrug-resistant tuberculosis during pregnancy. Int J Tuberc Lung Dis 15:547–550, 2011.
120. Centers for Disease Control and Prevention (CDC): Congenital syphilis—United States, 2003-2008. MMWR Morb Mortal Wkly Rep 59:413–417, 2010.
121. Centers for Disease Control and Prevention: Surveillance for viral hepatitis – United States, 2012. <www.cdc.gov/hepatitis/statistics/2012surveillance/commentary.htm#hepB>.
122. Lobstein S, Faber R, Tillmann HL: Prevalence of hepatitis B among pregnant women and its impact on pregnancy and newborn complications at a tertiary hospital in the eastern part of Germany. Digestion 83:76–82, 2011.
123. Shi Z, Yang Y, Ma L, et al: Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. Obstet Gynecol 116:147–159, 2010.
124. Arshad M, El-Kamary SS, Jhaveri R: Hepatitis C virus infection during pregnancy and the newborn period—are they opportunities for treatment? J Viral Hepat 18:229–236, 2011.
125. Yeung CY, Lee HC, Chan WT, et al: Vertical transmission of hepatitis C virus: Current knowledge and perspectives. World J Hepatol 6:643–651, 2014.
126. Al Arfaj AS, Khalil N: Pregnancy outcome in 396 pregnancies in patients with SLE in Saudi Arabia. Lupus 19:1665–1673, 2010.
127. Carvalheiras G, Vita P, Marta S, et al: Pregnancy and systemic lupus erythematosus: review of clinical features and outcome of 51 pregnancies at a single institution. Clin Rev Allergy Immunol 38:302–306, 2010.
128. Smyth A, Oliveira GH, Lahr BD, et al: A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol 5:2060–2068, 2010.
129. Ambrosio P, Lermann R, Cordeiro A, et al: Lupus and pregnancy—15 years of experience in a tertiary center. Clin Rev Allergy Immunol 38:77–81, 2010.
130. Gladman DD, Tandon A, Ibanez D, et al: The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. J Rheumatol 37:754–758, 2010.
131. Jara LJ, Medina G, Cruz-Dominguez P, et al: Risk factors of systemic lupus erythematosus flares during pregnancy. Immunol Res 60:184–192, 2014.
132. Chen CY, Chen YH, Lin HC, et al: Increased risk of adverse pregnancy outcomes for hospitalisation of women with lupus during pregnancy: a nationwide population-based study. Clin Exp Rheumatol 28:49–55, 2010.
133. Schramm AM, Clowse ME: Aspirin for prevention of preeclampsia in lupus pregnancy. Autoimmune Dis 2014:920467, 2014.

134. Lin P, Rhew E, Ness RB, et al: Adverse pregnancy outcomes and subsequent risk of cardiovascular disease in women with systemic lupus erythematosus. Lupus Sci Med 1:e000024, 2014.
135. Ostensen M, Clowse M: Pathogenesis of pregnancy complications in systemic lupus erythematosus. Curr Opin Rheumatol 25:591–596, 2013.
136. Lateef A, Petri M: Managing lupus patients during pregnancy. Best Pract Res Clin Rheumatol 27:435–447, 2013.
137. Triunfo S, Lanzone A: Impact of maternal under nutrition on obstetric outcomes. J Endocrinol Invest 38:31–38, 2015.
138. Solmi F, Sallis H, Stahl D, et al: Low birth weight in the offspring of women with anorexia nervosa. Epidemiol Rev 36:49–56, 2014.
139. Cardwell MS: Eating disorders during pregnancy. Obstet Gynecol Surv 68:312–323, 2013.
140. Keegan J, Parva M, Finnegan M, et al: Addiction in pregnancy. J Addict Dis 29:175–191, 2010.
141. Kanny D, Liu Y, Brewer RD, et al: Binge drinking—United States, 2011. MMWR Surveill Summ 62(Suppl 3):77–80, 2013.
142. Cannon MJ, Guo J, Denny CH, et al: Prevalence and characteristics of women at risk for an alcohol-exposed pregnancy (AEP) in the united states: estimates from the national survey of family growth. Matern Child Health J 19:776–782, 2015.
143. Centers for Disease Control and Prevention (CDC): Alcohol use and binge drinking among women of childbearing age—United States, 2006-2010. MMWR Morb Mortal Wkly Rep 61:534–538, 2012.
144. Hotham E, White J, Ali R, et al: Screening for use of alcohol, tobacco and cannabis in pregnancy using self-report tools. J Dev Orig Health Dis 3:216–223, 2012.
145. DeVido J, Boguic O, Weiss RD: Alcohol use disorders in pregnancy. Harv Rev Psychiatry 23:112–121, 2015.
146. Zhang K, Wang X: Maternal smoking and increased risk of sudden infant death syndrome: a meta-analysis. Leg Med (Tokyo) 15:115–121, 2013.
147. Werler MM, Yazdy MM, Kasser JR, et al: Maternal cigarette, alcohol, and coffee consumption in relation to risk of clubfoot. Paediatr Perinat Epidemiol 29:3–10, 2015.
148. Vinnars MT, Falkare S, Papadogiannakis N, et al: Placental pathology in smoking and non-smoking preeclamptic women. J Matern Fetal Neonatal Med 29:733–736, 2016.
149. Hayatbakhsh MR, Kingsbury AM, Flenady V, et al: Illicit drug use before and during pregnancy at a tertiary maternity hospital 2000-2006. Drug Alcohol Rev 30:181–187, 2011.
150. Gorman MC, Orme KS, Nguyen NT, et al: Outcomes in pregnancies complicated by methamphetamine use. Am J Obstet Gynecol 211:429.e1–429.e7, 2014.
151. Hekman KA, Grigorescu VI, Cameron LL, et al: Neonatal withdrawal syndrome, Michigan, 2000-2009. Am J Prev Med 45:113–117, 2013.
152. Epstein RA, Bobo WV, Martin PR, et al: Increasing pregnancy-related use of prescribed opioid analgesics. Ann Epidemiol 23:498–503, 2013.
153. Heil SH, Jones HE, Arria A, et al: Unintended pregnancy in opioid-abusing women. J Subst Abuse Treat 40:199–202, 2011.
154. Nezvalova-Henriksen K, Spigset O, Nordeng H: Effects of codeine on pregnancy outcome: results from a large population-based cohort study. Eur J Clin Pharmacol 67:1253–1261, 2011.
155. Wouldes TA, Woodward LJ: Maternal methadone dose during pregnancy and infant clinical outcome. Neurotoxicol Teratol 32:406–413, 2010.
156. Burns L, Conroy E, Mattick RP: Infant mortality among women on a methadone program during pregnancy. Drug Alcohol Rev 29:551–556, 2010.
157. Lind JN, Petersen EE, Lederer PA, et al: Infant and maternal characteristics in neonatal abstinence syndrome—selected hospitals in Florida, 2010-2011. MMWR Morb Mortal Wkly Rep 64:213–216, 2015.

CHAPTER 179: QUESTIONS & ANSWERS

179.1. A 28-year-old G2P1 at 26 weeks of gestation presents with a recurrent asthma flare. Vital signs are temperature, 36°C, heart rate, 110 beats/min, blood pressure, 120/60 mm Hg, respiratory rate, 28 breaths/min, and O_2 saturation, 96%. She has diffuse expiratory wheezes. Arterial blood gas reveals Po_2 = 90 mm Hg, Pco_2 = 40 mm Hg, and pH = 7.34. Which of the following statements best describes the issues in management with this patient?

A. Corticosteroids are contraindicated.
B. Inhaled β-agonists are first-line therapy.
C. Most patients with asthma improve during pregnancy.
D. She has a metabolic acidosis.
E. Treatment and discharge are likely.

Answer: B. β-Agonists followed by corticosteroids are the mainstay of asthma therapy during pregnancy. During pregnancy, one-third of asthmatics worsen, one-third improve, and one-third stay the same. Blood gas interpretation must take into account the so-called normal alkemia of pregnancy, with a Pco_2 of 30 to 32 mm Hg and a compensatory HCO_3 level of 18 to 20 mEq/L. This patient has a relative hypoventilation and may indeed need admission for close observation.

179.2. Which of the following statements best describes treatment for hypertension in pregnancy?

A. Angiotensin-converting enzyme inhibitors are second-line agents.
B. Diuretics are contraindicated in the third trimester.
C. Hydralazine is a useful venodilator.
D. Labetalol is a first-line oral agent.
E. Sodium nitroprusside is the parenteral agent of choice.

Answer: D. First-line oral and parenteral agents are hydralazine and labetalol. The former is an arterial dilator. Most antihypertensives are useful in pregnancy; angiotensin-converting enzyme inhibitors and receptor blockers are the exception. Diuretics are second-line agents. Nitroprusside is a second-line agent due to concerns for fetal cyanide toxicity.

179.3. Which of the following statements best describes risk factors for acute myocardial infarction (AMI) and pregnancy?

A. Anemia is not a risk factor.
B. Gestational diabetes does not increase risk.
C. Hypotension is an important risk factor.
D. Maternal age is inversely associated with risk.
E. Maternal smoking increases the risk.

Answer: E. Maternal smoking increases the risk. AMI is rare but may occur. Up to 29% of cases have normal coronaries one their angiogram. Risk factors are anemia, diabetes, hypertension, old age, thrombophilia, and smoking. Atherosclerotic lesions are the more likely cause antepartum, whereas coronary dissection and vasospasm are more likely causes postpartum.

179.4. Which of the following statements best describes issues in the evaluation of diabetes mellitus in pregnancy?

A. Diabetic ketoacidosis (DKA) in pregnancy always presents with hyperglycemia and a low pH.
B. Patients with gestational diabetes usually require medical therapy to achieve adequate glycemic control.
C. Standard management of non–insulin-dependent diabetes in pregnancy is with continued use of oral medications.
D. The American Congress of Obstetricians and Gynecologists recommends universal screening for gestational diabetes.
E. The risk of malformations and pregnancy complications is significantly increased in patients with insulin-dependent disease as opposed to those with pregravid, non–insulin-dependent diabetes.

Answer: D. The American Congress of Obstetricians and Gynecologists recommends universal screening for pregnant women to achieve prompt diagnosis and minimize related complications. Insulin-dependent diabetes mellitus (IDDM) and non–insulin-dependent diabetes mellitus (NIDDM) place the gravida at increased risk for poor pregnancy outcomes, with the risk being related to inadequate glycemic control. Although patients with

IDDM and NIDDM are typically managed with insulin during pregnancy, patients with gestational diabetes often achieve adequate control of their blood glucose level with diet alone. DKA is a potential complication of all forms of diabetes during pregnancy and may present with euglycemia and a minimal change in pH.

179.5. Which of the following statements best describes issues in the management of the pregnant patient with human immunodeficiency virus (HIV)?

A. Antiretroviral therapy is not appropriate in the first trimester of pregnancy with the exception of efavirenz, which is contraindicated.

B. Elective cesarean section is not indicated for all gravidas with HIV and a viral load greater than 1000 copies/mL.

C. Postnatal zidovudine therapy in the infant is necessary when the mother has received appropriate antepartum and intrapartum antiretroviral therapy and has a viral load less than 1000 copies/mL.

D. The risk of perinatal transmission of HIV is high in the setting of routine screening, intrapartum antiretroviral therapy, and elective cesarean section for patients with a viral load greater than 1000 copies/mL.

Answer C. Recommended care for HIV during pregnancy includes intrapartum antiretroviral therapy, postnatal zidovudine prophylaxis, standard treatment for opportunistic infections, and cesarean section for all patients with a viral load greater than 1000 copies/mL. It is appropriate to begin antiretroviral therapy during the first trimester, although it is recommended that these patients be managed by an infectious disease specialist. Postnatal zidovudine is recommended for all infants born to mothers with HIV.